OFFICIAL JOURNAL OF THE INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION

International Assembly—Municipal Auditorium, Milwaukee, Wisconsin, November 14 to 17

*Volume 17, Number 6*

**JUNE 1955**

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# Postgraduate Medicine

*Volume 17 · Number 6*

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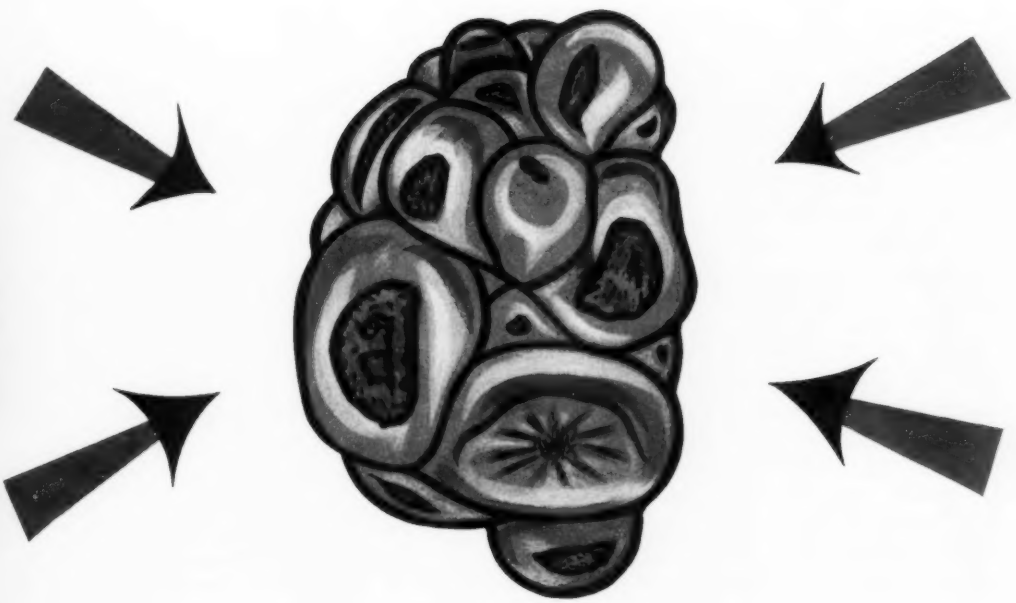
# CANCER • *A Special Issue*

R. LEE CLARK, JR., M.D.
*Guest Editor*



# Improving Cancer Care

R. LEE CLARK, JR.*

*Guest Editor*

THE results of the treatment of cancer patients reported in the current medical literature do not accurately reflect current cancer cures. The unreported results of treatment and the associated cure rate for cancer are much worse.

Reports of cancer treatment are usually published from medical centers or by individuals who are interested sufficiently to follow the patient with cancer, after treatment, for a long enough time to ascertain the results. Most patients with cancer, however, die without the benefit of this kind of treatment. At the community level, the average patient receives the treatment that is most expedient for a particular community, ofttimes with inadequate facilities or medical skills. Also, many patients do not present themselves for treatment until the disease is at an advanced stage; or, if they do present themselves for treatment in an earlier stage, the disease may not be recognized until it has become obvious. Treatment is frequently begun with the physician already handicapped by extension of the disease; further, the initial treatment is often inadequate. Follow-up procedures are not instituted until symptoms of the disease reappear; and often they include only the administration of pain control drugs in the terminal phases or emergency care for hemorrhage or obstruction immediately prior to death.

The only hope of relief of this condition in the near future lies with the physician at the community level. His participation can be enlisted immediately by following the recent recommendations of the American College of Surgeons' Cancer Committee. This organization has suggested the establishing of *record registries* and *follow-up clinics* in any accredited hospital where cancer patients are seen. Better care begins with a knowledge of what is being attained by the present methods of care. When a physician learns that poor results are being obtained, his professional interest is aroused to improve the situation. When he observes the results of treatment at follow-up clinics, the inadequacies soon become apparent. At the same time, medical education must point out the source of errors in the initial recognition of cancer in the patient, and the necessity for adequate treatment of the patient in the initial therapeutic approach. Physicians who have graduated since World War II have had the opportunity to learn the possibilities of adequate treatment by special training in their medical schools through the Cancer Teaching Grants of the National Cancer Institute. Also, more and more physicians with adequate specialty training are to be found at the community level. With the cancer clinic plan being emphasized by the American College of Surgeons, there should be increasingly less difficulty in securing the co-ordinated advice and opinion of the various necessary specialists regarding any individual case.

By applying the principles of surgery and irradiation that we now know and have available in trained and competent hands, the cure rate for cancer at the community level, particularly those cancers of accessible sites, should be doubled. Cancers of accessible sites constitute at least 70 per cent of curable cancer.

The articles in this issue of POSTGRADUATE MEDICINE are directed toward increasing the participation of the physician at the community level, in the earlier recognition of malignant disease, and in his securing for his patients the best of the currently acceptable methods of treatment.

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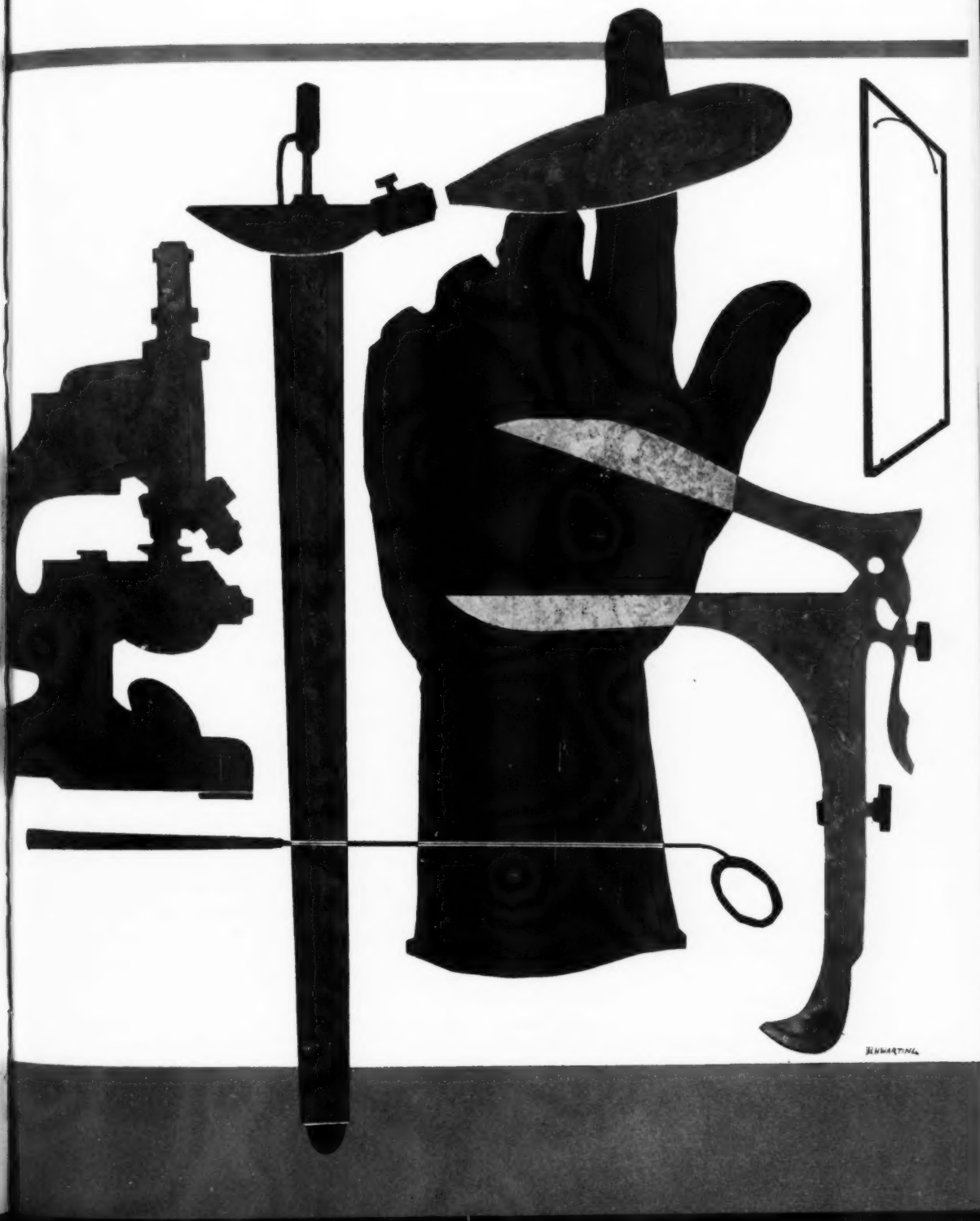
# DIAGNOSIS



# Diagnosis of Carcinoma of the Lung

WALTER J. BURDETTE*

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WALTER J. BURDETTE

The five year survival rate in most cases of bronchogenic carcinoma is 5 to 10 per cent.[1-6] Although thoracotomy is now performed more frequently, and although the type of operation is more radical, appreciable improvement in this figure is unlikely without earlier diagnosis. The practitioner faces the task of separating patients with serious organic disease from patients with similar complaints. Cancer of the lung is no exception, and, in addition, the most favorable situation for treatment is one in which there are no symptoms.[5] A suggested plan for arriving at a diagnosis in this disease will be outlined after I have given a brief résumé of the current status of bronchogenic carcinoma in a city with one of the highest rates for this type of cancer.

### *Incidence of Bronchogenic Carcinoma*†

The number of bronchogenic carcinomas per 1000 males admitted to Charity Hospital within the past six years was 7.9, which constituted 15.9 per cent of all cancers in males. In 23 (3.1 per cent) of the total number of cases (733), the tumor was either the first or second of two separate neoplasms. A glance at figure 1 will verify not only that bronchogenic cancer is a disease found after the age of 40, but also that it develops in the 10 preceding years with alarming frequency (24 cases). Distribution of cases by sex and race (91.4 per cent in white males and 90.8 per cent in Negro males, and 8.6 per cent in white females and 9.2 per cent in Negro females) shows the usual discrepancy between the sexes

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Based on study made with aid of a grant from the National Cancer Institute, U.S. Department of Health, Education, and Welfare.

†The help of Mrs. V. L. Wogan, Jr. and her staff in the Tumor Registry of Charity Hospital is gratefully acknowledged.

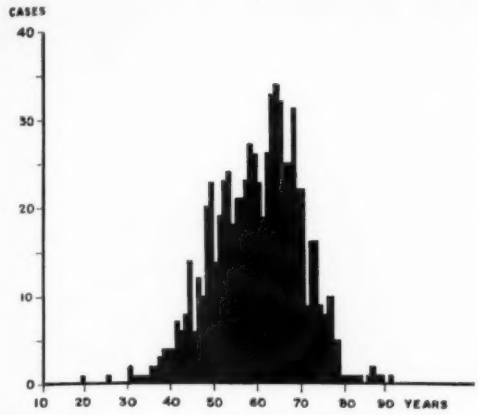



FIGURE 1. Age incidence of bronchogenic carcinoma.

but no difference in racial incidence. The incidence of squamous and anaplastic carcinomas and adenocarcinoma was 70.4, 22.6, and 7 per cent respectively in males; and 47.4, 31.6, and 18.4 per cent in females. At the time of the original diagnosis, the neoplasm appeared to be localized in 28.7 per cent of the cases, but remote metastasis was demonstrable in 24.5 per cent of cases in which the stage of the disease was recorded.

### *History*

After a silent period, symptoms of carcinoma of the lung usually result from local extension with pulmonary complications, from metastasis, and finally from systemic effects of the cancer. Cough, transient pain in the chest, wheezing, influenzalike symptoms and hemoptysis are not unusual. With invasion of branches of the vagus nerve, hoarseness and digestive symptoms may appear. Dyspnea, weakness, anorexia, emaciation and symptoms related to the central nervous system may follow as the disease becomes more advanced. In obtaining the patient's history, geographic information may be useful in distinguishing cancer from coccidioidomycosis and blastomycosis.

### *Physical Examination*

Each patient expects and deserves a thorough physical examination, including percussion and auscultation of his chest. The stethoscope is by no means outmoded. Wheezing, rhonchi, suppressed breath sounds, and areas of dullness may give the first indication of disease. A careful search for firm, discrete lymph nodes in the axillae and supraclavicular fossae may lead to a positive diagnosis by biopsy. Cyanosis and clubbing of the fingers usually do not occur until complications ensue. An interesting accompaniment of pulmonary carcinoma is the arthritis which is encountered at times and which promptly disappears with resection of the lesion.

### *Roentgenologic Examination*

Roentgenologic examination is invaluable for screening and diagnosis, and a lateral roentgenogram should be made routinely. Oblique and stereoscopic roentgenograms may also be helpful. Laminagrams will resolve confusing shadows, visualize cavities, and delineate the site of bronchial obstruction in selected cases (figure 2). Fluoroscopy is useful for determining diaphragmatic motion and for detecting pulsations. Pneumothorax, combined with aspiration of fluid when necessary, may aid in distinguishing parenchymal from mediastinal and parietal lesions, and gravitational changes in the fluid with changes in position may occasionally be helpful. Pneumoperitoneum sometimes distinguishes a pulmonary neoplasm from an infradiaphragmatic mass or a diaphragmatic hernia.

Since bronchograms often obscure the subsequent course of the disease, a good rule to follow is to arrange bronchoscopy as the last diagnostic study and to remember that operation may be delayed if LIPIODOL® is used. Angiograms have been of value in distinguishing vascular lesions such as aneurysms from carcinoma, but in my hands they have not helped much in determining the resectability of the neoplasm.

There is no characteristic roentgenographic picture of carcinoma of the lung which clearly distinguishes it invariably from other pulmonary lesions. Indeed, the picture often is that of the secondary effects of the tumor rather than that of tumefaction, and the diagnosis may easily be overlooked by mistaking the superimposed condition for the primary

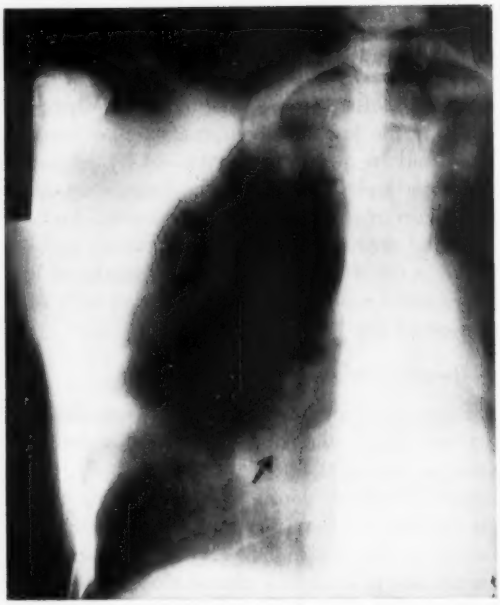


FIGURE 2. Laminagrams such as this one may show the site of obstruction by carcinoma (arrow).

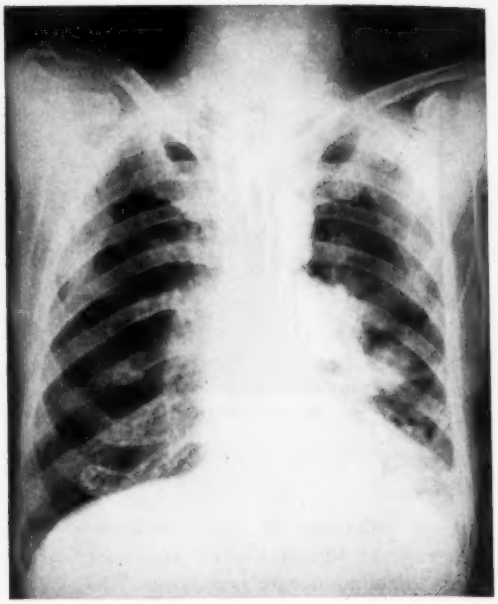


FIGURE 3. Distant metastatic lesions contraindicate operation. Both primary carcinoma and osteolytic clavicular metastasis are visible in this roentgenogram.

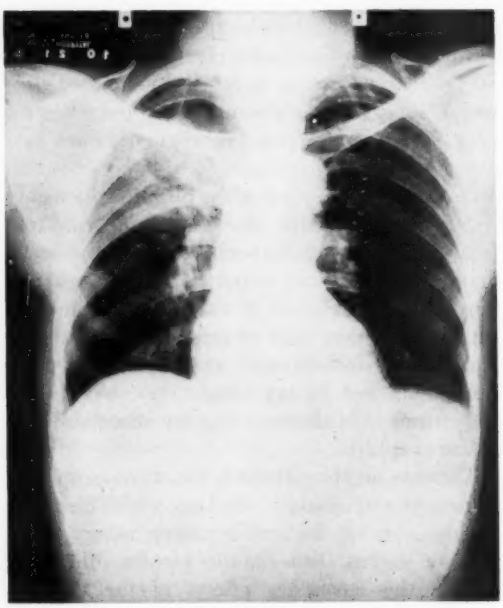
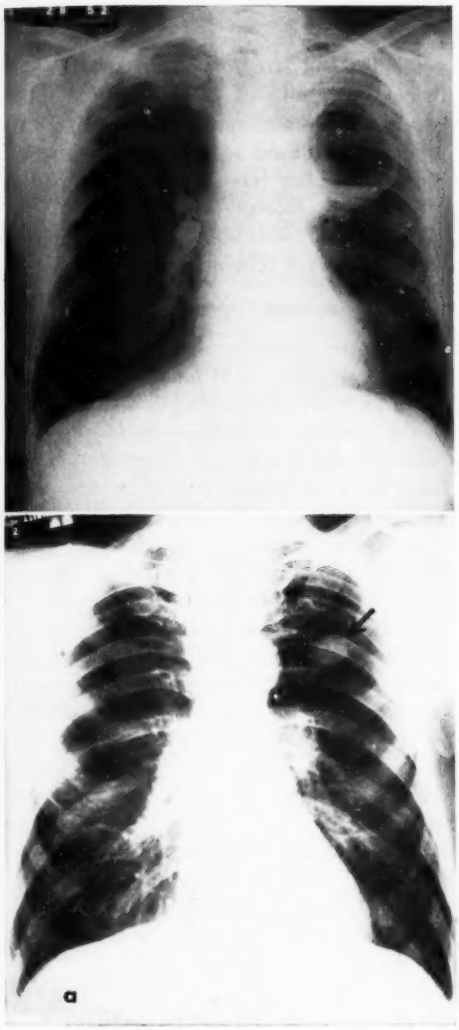
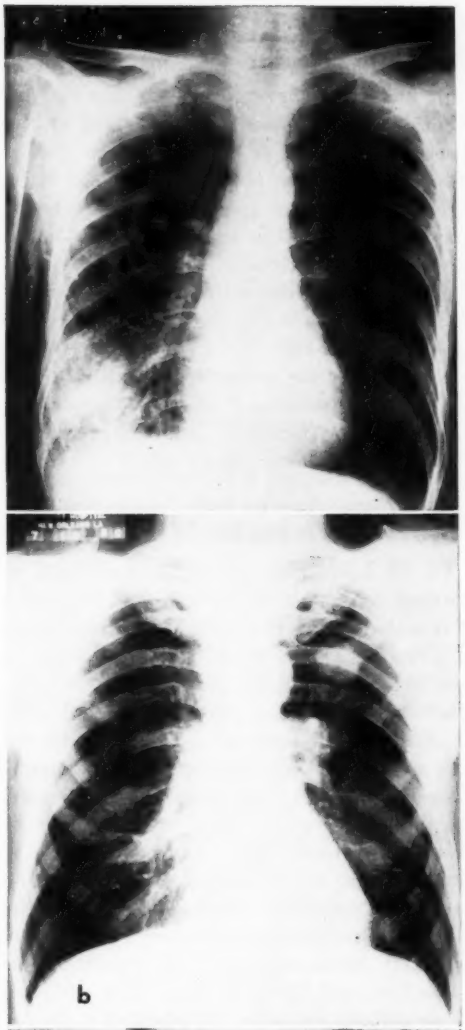


FIGURE 4. Bronchogenic carcinoma appears most frequently in upper lobes where it may simulate tuberculosis as in this case.

FIGURE 5. Pneumonitis may be a complication of carcinoma of the lung and may deceptively regress temporarily as a result of antibiotic therapy.











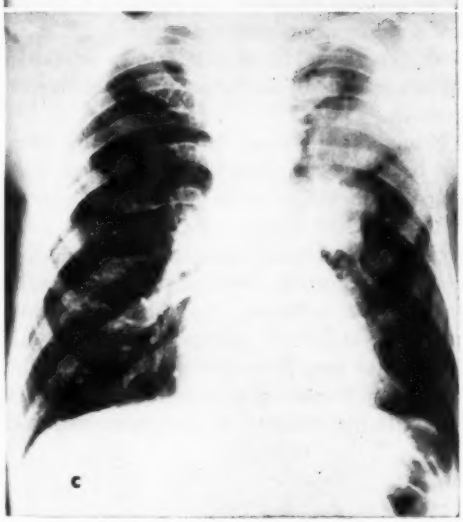



FIGURE 6, *top, left.* Cavitation may obscure an underlying carcinoma. This patient's neoplasm is an example.

FIGURE 7, *top, right.* Bronchiectasis and carcinoma may be confused. Bronchograms are helpful in diagnosing bronchiectasis but obscure the subsequent course of the disease and may delay operation. This patient had a carcinoma.

FIGURE 8. A solitary lesion such as that in (a) *arrow* is the most favorable for operation. Following this type of lesion (b) in the hope of regression is exceedingly unwise, as shown in (c).

disease. Pneumonitis, bronchial obstruction with atelectasis or emphysema, abscess and pleural effusion often occur in cases of this disease. Elevation of the diaphragm due to involvement of the phrenic nerve and osteolytic lesion of ribs and clavicles (figure 3) may occur in cases in which the carcinoma is advanced. Limitations of space do not permit a discussion of differential diagnosis, but the most common diseases to be considered are tuberculosis (figure 4); pneumonitis (figure 5); infections due to bacteria, viruses or fungi; chronic pulmonary abscess (figure 6); bronchiectasis (figure 7), and solitary lesions such as tuberculoma (figure 8).

### *Exfoliative Smears and Microbiologic Studies*

Of all laboratory studies, examination of the sputum is most informative and most easily repeated. Examination of exfoliative smears may double the number of cases in which positive diagnoses can be made before surgery. Microbiologic studies may also be indicated at times, and the material utilized includes not only sputum but also fasting gastric contents, material obtained from abscesses and sinuses, and biopsy material. Solid material may be ground to proper consistency after a portion has been sent for histologic examination. Immediate examination saves time and may be the only examination of value, since organisms may not be recovered from cultures because they are dying or have been obscured by secondary invaders. Addition of a 10 per cent solution of potassium hydroxide will clear fresh smears, and fixed material can be stained advantageously by the Gram and Ziehl-Neelsen methods.

Primary pulmonary involvement by fungi and bacteria will often lead to disaster if resected, particularly in the acute stage. In cases of this type of disease, it is wiser to await results of cultures and animal inoculation. Seabury[7] recommends Petragnini's or a similar medium for culturing the tubercle bacillus and fungi at 37° C., except for *Actinomyces bovis* which may be recovered from anaerobic cultures on Bacto-brain-heart infusion agar at 37° C. If the material is contaminated, both penicillin and streptomycin should be added in concentrations of 100 units per milliliter, except for the omission of streptomycin when tubercle bacilli are sought. Animals are killed four weeks after inoculation unless they have died sooner. Except for diagnosis of blastomycosis and coccidioidomycosis, serologic tests are not yet reliable.

### *Bronchoscopy*

The procedures mentioned so far may be done in an office or clinic. If carcinoma still is a possibility, the patient should be admitted to the hospital. Bronchoscopy is indicated in cases in which a tissue diagnosis cannot be made by other means, particularly in cases in which an exploratory operation is to be performed. Gentleness and psychologic preparation of the patient beforehand are important contributions to the success of this procedure. The relaxation which comes with gaining the patient's confidence is invaluable. The results of biopsy will be positive in approximately 40 per cent of cases of bronchogenic carcinoma. In the remainder, the negative result will be due to inaccessibility of peripheral lesions and those in the upper lobes. Indirect evidence of tumor, such as narrowing or displacement of the bronchi and blunting of the carina, is often very helpful. Bronchial washings will supply additional material for culture and exfoliative smears. The presence of paralysis of the vocal cords also may be verified. This is more common on the left side because the recurrent nerve extends lower on that side as it passes the aorta.

### *Biopsy*

Biopsy of axillary and cervical lymph nodes of suspicious size and consistency may avert a futile operation. Needle biopsy of primary or metastatic lesions is permissible in order to establish a histologic diagnosis before nonsurgical therapy, but it should not be performed if an operable lesion is present, since viable cells may be disseminated along the needle tract. Material centrifuged from pleural fluid also may contain malignant cells. When a tumor is visible on the pleural surface, thoracoscopy may be utilized after pneumothorax

to visualize the lesions and to obtain a specimen for biopsy. This procedure is used in unusual cases of bronchogenic lesions only.

### *Search for Metastases*

One should always remember that this disease may be either primary or metastatic. Besides views of the chest, roentgenograms most likely to show osseous metastasis from bronchogenic carcinoma are those of the skull, pelvis and lumbar segment of the spinal column. Careful physical examination of the male and female genital organs, pyelograms, and barium studies of the alimentary tract may be helpful in locating primary neoplasms which have metastasized to the lung. A hopeless attitude toward metastatic carcinoma of the lung is not warranted, since the survival rate after extirpation of a solitary metastatic lesion when the primary lesion is controlled compares favorably with that after removal of bronchogenic carcinoma.[8]

### *Thoracotomy*

No matter how astute the clinician, suspected lung cancer cannot be diagnosed preoperatively in some cases. When this point is reached, an exploratory operation should be performed immediately. Time is really the most important factor in management of this disease; delay may cost the patient his chance for survival. This cancer should be treated as any other; biopsy of the lung should be performed (this may involve lobectomy), and the lung should be removed if the diagnosis is verified. Two common errors are observation of solitary lesions for prolonged periods (figure 8) and mistaking carcinoma for pneumonia (figure 5). In the former instance, the physician has no contemporary support for such management; in the latter, he is usually misled by temporary regression of the pneumonitis with antibiotic therapy, which also may occur when carcinoma is present. Fortunately, the dilemma of the diagnostician has been somewhat relieved in recent years by demonstration that resection is the treatment of choice for many of the conditions with which carcinoma of the lung is confused.

### *Summary*

Time lost in disorganized studies and lack of resolution about the proper course to follow in diagnosing carcinoma of the lung are now inexcusable. The diagnostic study should include a history, physical examination, roentgenologic examination, exfoliative smears, microbiologic investigation, bronchoscopy, biopsy, a search for metastatic lesions, and thoracotomy. Adherence to such a plan, prompt decision, and early operation will undoubtedly lead to more cures.

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# Esophageal Carcinoma

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DYSPHAGIA is a broad term including any and all difficulties in swallowing and may be caused by a variety of organic diseases. It is an extremely important symptom and always deserves prompt and complete investigation. Fortunately, in most instances, the cause of dysphagia can be determined readily by diagnostic means available to all physicians.

One of the commonest causes of dysphagia in the adult patient is carcinoma of the esophagus. At the present time, dysphagia is the most important and earliest symptom of esophageal carcinoma. Investigation of dysphagia involves, first, a careful history of the patient's symptoms, its duration, its character, and the circumstances under which it has occurred. The dysphagia that results from carcinoma of the esophagus differs greatly from the dysphagia caused by esophageal diverticulum, cardiospasm or myasthenia gravis.

The results of physical examination of patients complaining of dysphagia are likely to be essentially negative except for evidence of loss of weight. However, a valuable method of physical diagnosis which is often neglected is the simple expedient of watching the patient drink a few swallows of water. Frequently, more can be learned from this simple observation than from any verbal description of the symptoms given by the patient.

Thorough roentgenologic investigation of the esophagus in every case of dysphagia is essential. This should include both fluoroscopic and roentgenographic studies. In competent hands this examination will provide an accurate diagnosis of the nature and site of the esophageal obstruction in most instances. Roentgenologic diagnosis of carcinoma of the esophagus is remarkably accurate when dysphagia is present. This is true because dysphagia usually does not occur in cases of car-

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cinoma of the esophagus until the lesion involves half to three-fourths of the circumference of the esophagus and is sufficiently large to be recognized easily.

The final diagnostic study that must be carried out in all patients suspected of having carcinoma of the esophagus is the endoscopic procedure, esophagoscopy. This permits direct visualization of the lesion and removal of a specimen of the lesion for pathologic examination. In addition, endoscopy provides valuable information regarding the extent of the growth and its fixation to surrounding structures. Bronchoscopy as well as esophagoscopy should be carried out in all cases in which carcinoma of the esophagus occurs at or above the level of the bifurcation of the trachea. This procedure will determine whether the carcinomatous lesion has involved the posterior wall of the trachea, thus providing information regarding the operability of the lesion. Occasionally, cytologic examination of smears of esophageal secretions obtained at the time of esophagoscopy will provide proof of the presence of esophageal carcinoma even when the results of biopsy are negative.

With the diagnostic methods now available, it is possible to establish a diagnosis of carcinoma of the esophagus readily among patients who have dysphagia. However, as has been indicated previously, dysphagia does not occur until a fairly extensive lesion has developed. It is indeed unfortunate that there are no really early recognizable symptoms of carcinoma of the esophagus to call attention to the presence of this lesion. By means of the best diagnostic methods, roentgenologic examinations and esophagoscopy, detection of small early neoplasms of the esophagus is possible, but the physician rarely has an opportunity to study the neoplasms at this stage.

If carcinoma of the esophagus is to be detected early, when conditions for surgical resection are favorable, some means must be developed whereby its presence can be recognized. By the time symptoms are produced, the early stages of development are past. Until such means become available, it is essential that dysphagia be investigated promptly and thoroughly whenever it occurs.


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# Cancer of the Breast

MURRAY M. COPELAND*

*Georgetown University Medical Center, Washington, D.C.*

MURRAY M. COPELAND

MICROSCOPIC study is the only reliable basis on which to make the final diagnosis of mammary cancer, but clinical diagnosis achieves a fair degree of accuracy in most instances. If one takes into account the age of the patient; whether the lesion is single, multiple or diffuse; the site of the lesion; its characteristics on palpation; the presence or absence of inflammation, signs, and evidence of injury, the number of possibilities in the differential diagnosis are definitely limited.

The malignant lesions of the breast and the benign lesions with which they may be confused are listed in table 1.

Clinical judgment must rest on the individual experience of the doctor, but the following rules of procedure are valuable in the diagnosis and treatment of lesions of the breast. Some of these rules apply primarily to the examining physician and others to the consulting surgeon.

1. Do not overlook early pregnancy in taking the menstrual and marital history; this may be responsible for the sudden growth of a benign or malignant tumor.

2. Do not fail to interrogate the patient with reference to puerperal mastitis. Cancer which develops in the scar of lactation mastitis has a grave prognosis.

3. Do not neglect a careful routine examination of the breasts.

4. Do not neglect transillumination (nonpalpable tumors may be revealed).

5. Do not omit a pelvic examination (it is important in the diagnosis of breast dysplasia).

6. Do not omit a serologic test for syphilis.

7. Do not omit roentgenograms of the chest; a skeletal survey if indicated.

8. Do not give endocrine or radiation therapy until the appropriate diagnosis is made.

9. Do not neglect microscopic examination of smears of any discharge from the nipple.

10. The possibility of cancer is not ruled out without biopsy of a suspicious nodule by a competent surgeon.

*Director, Department of Oncology, Georgetown University Medical Center, Washington, D.C.

TABLE 1

MALIGNANT LESIONS OF BREAST AND BENIGN LESIONS WITH WHICH THEY MAY BE CONFUSED

| MALIGNANT LESIONS | BENIGN LESIONS |
|---|---|
| Cancer in residual lactation mastitis | Chronic puerperal mastitis |
| Early infiltrating cancer | Fat necrosis; fibrosing adenoma in adenosis |
| Comedo or duct cancer | Duct adenoma in adenosis |
| Mammary carcinoma or sarcoma | Fibroadenoma in pregnancy or lactation; giant myxoma |
| Papillary cancer | Benign cystic papilloma |
| Paget's cancer | Ampullary papilloma |

FIGURE 1. Palpation of supraclavicular region.

11. The interpretation of smears and biopsy specimens should be made by a competent pathologist.

Great care must be exerted to study the breasts, particularly in a routine physical examination. Casual palpation of the breasts will fail to reveal significant lesions.

The examination should begin with inspection of the breasts, supraclavicular regions and axillae with the patient in the sitting position, her hands above her head and by her sides. The examination must be conducted in a good light. Any deviation of the nipples from the normal, and any alteration of the contour of the breasts or configuration of the supraclavicular regions or axillae may betray the presence of breast cancer. Early changes are frequently difficult to observe.

Inspection is followed by palpation of the breasts and the regional lymph nodes. The supraclavicular region (figure 1) and axillae (figure 2) are best examined with the patient in a comfortable sitting position. It is essential that the pectoral muscles be relaxed (figure 2). Gentle palpation will reveal more than will a tense digging in the axillae. At best, axillary palpation is notoriously inaccurate in determining the status of involvement of the axillary lymph nodes.

The breasts should be gently examined with

FIGURE 2. Palpation of axillary region. Note pectoral muscle relaxation is obtained by resting patient's arm on that of the examiner.

the patient in the reclining position. The shoulder related to the breast being examined should be elevated by a folded sheet. This maneuver flattens the breast on the thorax and permits a better distribution of breast tissue for palpation (figures 3 and 4). The breast should be gone over thoroughly and in an orderly fashion with the relaxed extended fingers of one hand. In palpating the medial half of the breast, the patient's arm should be raised above her head in order to provide a flatter surface for palpation.

Care should be taken to palpate the parasternal area, the infraclavicular region, along the edge of the latissimus dorsi muscle and the lateral edge of the pectoralis major muscle. Breast tissue often extends beyond the confines of the obvious anatomic site. One should not neglect to palpate bimanually the lower portions of pendulous breasts with the patient in the sitting position.

The consistency, discreteness and mobility of the tumor are important in determining the diagnosis. A firm indurated nodule, not sharply circumscribed and relatively fixed, suggests that the lesion is cancer. Many well-circumscribed cancers, however, are mistaken for benign lesions.

*Retraction* or dimpling of the skin is an almost positive sign of cancer (exceptions are fat necrosis and induration following trauma or infection). The desmoplastic reaction about carcinoma foreshortens the fascial septa related to the skin or nipple and produces dimpling or retraction.

Skin retraction in advanced disease is readily noted. In cases of small, early carcinoma, the disease often can be demonstrated only by certain maneuvers. Raising the patient's arms above her head may reveal unnoticed asymmetry of the breasts or skin retraction. Lifting or compression of the breast on both sides of the carcinoma (figure 5) may cause a dimple to appear. Pectoral muscle contraction initiated by the patient by pressing her hands against her hips may cause elevation of the diseased breast as compared with the unaffected breast, and it may also demonstrate dimpling and nipple deviation (figure 6). The forward-bending maneuver (Auchincloss-

FIGURE 3. Palpation of the medial side of the breast. Note the arm raised above the head.

FIGURE 4. Palpation of the lateral side of the breast. Note the arm at the side.

Haagensen maneuver) in which the patient is asked to bow forward from the hips, keeping the chin extended—the examiner supporting the arms which are extended forward as he sits before her (figure 7)—tends to cause normal breasts to fall freely away from the chest wall. If carcinoma is present, the surrounding fibrosis fixes the diseased breast to the chest wall in varying degrees, producing asymmetry which may be seen from the front or side of the breast. The size and shape of the breasts alter the effectiveness of this maneuver.

*Erosion of the nipple* is highly significant and warrants a presumptive diagnosis of cancer (Paget's disease) until proved otherwise. An associated mass may or may not be palpated in the depth of the breast.

*Discharge from the nipple* may be physi-

FIGURE 5. Dimple demonstrated by compressing the breast on both sides of the carcinomatous area.

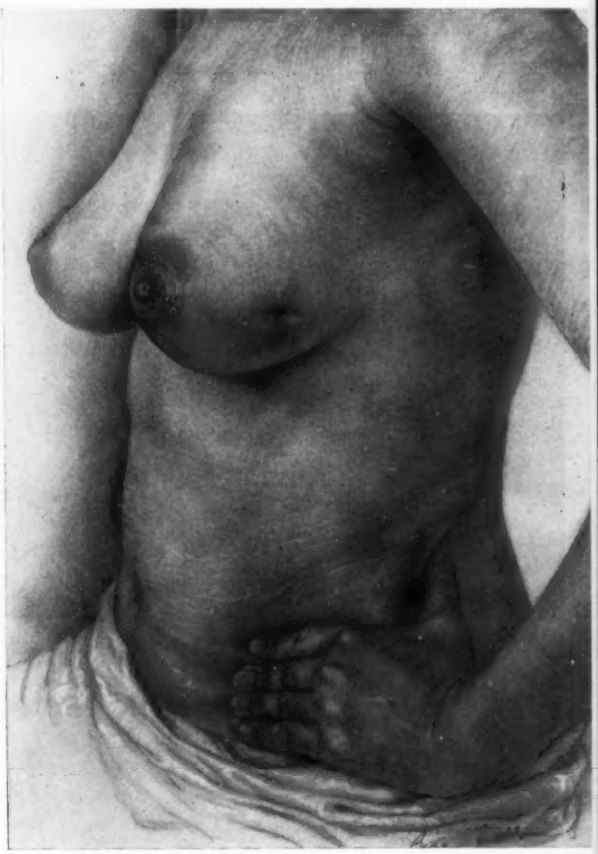

FIGURE 6. Pectoral muscle contraction maneuver. Note dimple in skin of breast.

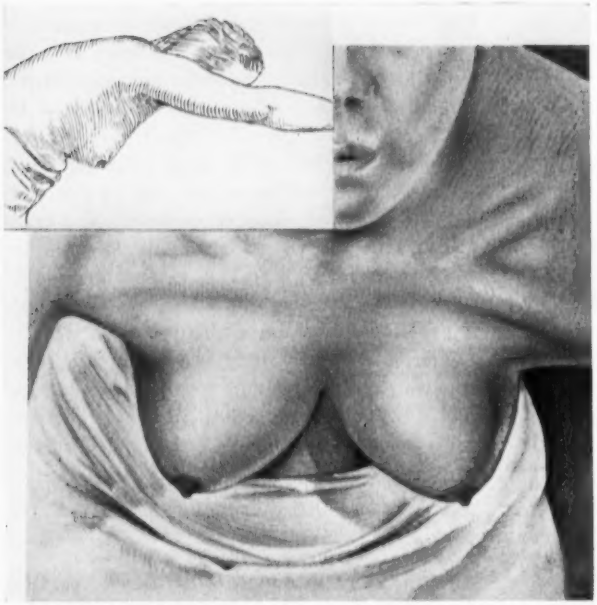

FIGURE 7. The forward-bending maneuver demonstrating a change in contour of the left breast.

FIGURE 8. Transillumination of breast in a completely dark room. Note the irregularity of the shadow. At operation the lesion proved to be organized hemorrhage about a papilloma.

ologic or pathologic. The character of the discharge is important. The milklike discharge seen after lactation or even years later is usually harmless. Exudate from inflammation of the ducts occurs and may be confirmed by examination of a smear. A thin discharge of a clear, yellowish or brown color, or a discharge of bloody content usually connotes some phase of epithelial proliferation. Bloody discharge frequently requires repeated examination to identify the site of the local pathologic condition (usually intraductal papilloma). Such a lesion should be excised. The yellowish and brown discharges often reflect a general endocrine hyperplasia and have no special neoplastic significance.

Other signs of carcinoma include circulatory disturbances, such as hyperemia and edema of the skin. These changes, of course, may be seen in cases of infection or occasionally in cases of benign tumor.

Transillumination (figure 8) of the breasts has proved to be of only limited value. When a definite shadow is seen, the presence of carcinoma is not proved and further diagnostic steps are necessary.

# Cancer of the Skin and Melanoma

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ONE need only look through the pages of a standard textbook on dermatology to realize the multiplicity of lesions that involve the skin. Many of these lesions are merely the dermal manifestations of some systemic disease; others, the result of various types of irritation; and still others, primary diseases of the skin as an organ. The malignant lesions arising in the dermis and its appendages may also assume many different appearances. The doctor in his office is confronted, first, with the problem of diagnosis, and, secondly, with the problem of what advice to give the patient once the diagnosis is determined.

THEODORE R. MILLER

Even though the lesion is clearly visible, it is amazing that there are still approximately 5000 deaths a year in the United States from malignant tumors of the skin. Errors in diagnosis, failure to make a diagnosis of a skin lesion in the presence of another illness, and the tendency to ignore the premalignant dermatoses, as well as the choice of inappropriate and inadequate treatment, all contribute to this mortality rate.

Skin cancer accounts for 17 to 18 per cent of all cancers in the male. In the female it is surpassed only by cancer of the breast and of the genital organs. As in all other forms of cancer, early diagnosis and prompt and appropriate treatment afford the best prognosis. The physician has a great opportunity in prophylaxis in malignant tumors of the skin (table 1) as there are many definitely premalignant dermatoses (table 2) which require relatively simple measures for their eradication as compared with the measures necessary to treat fully developed malignant lesions.

An attempt at clinical diagnosis should be made, though the physician will often be surprised at the wide variance between the clinical impression and the pathologic report. In

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TABLE 1

CARCINOMAS AND SARCOMAS OF THE SKIN

| |
|---|
| Carcinomas: |
| Basal cell epithelioma |
| Basosquamous cell epithelioma |
| Squamous cell epithelioma |
| Paget's disease |
| Bowen's disease |
| Malignant melanoma |
| Sarcomas: |
| Kaposi's sarcoma |
| Lymphosarcoma |
| Neurogenic sarcoma (arising in the neurofibroma of von Recklinghausen's disease) |
| Lymphoblastoma |
| Dermatofibrosarcoma |

TABLE 2

PRECANCEROUS DERMATOSES

| |
|---|
| Cicatrix |
| Cornu cutaneum |
| Erythroplasia |
| Farmer's or sailor's skin |
| Keratoses: |
| Arsenical |
| Seborrheic |
| Senile |
| Occupational (due to tar, pitch, oil, carbon, etc.) |
| Kraurosis vulvae |
| Leukoplakia |
| Lupus erythematosus |
| Lupus vulgaris |
| Nevi |
| Radiodermatitis |
| Sebaceous cysts |
| Syphilis (syphilitic leukoplakia, interstitial glossitis, syphilitic scars) |
| Ulcers (long-standing) |
| von Recklinghausen's disease (multiple neurofibromatosis) |
| Xeroderma pigmentosum |

the examination of the patient, the entire skin surface should be exposed and examined in a good, natural light. The subtending, node-bearing areas should be carefully palpated for any adenopathy. History taking is largely important in determining the length of time that the lesion has been present and the character of the change that has taken place or that has drawn the attention of the patient to the lesion. The presence of hair in a pigmented lesion usually suggests benignity; ulceration and bleeding suggest malignancy. Pigmentation may be due to exogenous pigment or may be a function of the tumor, as in malignant melanoma, though the lack of pigment does not rule out the diagnosis of malignant melanoma since the tumor may be growing too rapidly to produce much pigment.

Once the history and physical examination of the lesion have been completed, the most important diagnostic measure must be carried out. Without biopsy, the diagnosis remains a guess and forms a poor basis for rational therapy. It is my opinion that surgical biopsy of an ulcerated lesion is a perfectly safe procedure, since the containing membrane has already been broken by the ulceration. Usually, this can be accomplished without anesthesia if the specimen is taken from the fungating portion of the tumor, since most ulcerating lesions have not developed any sensory nerve supply to the growing edge. Small biopsy forceps which will remove a section of 2 to 4 mm. are adequate in most instances. The tissue should be placed on a piece of white blotting paper and a drop of FORMALIN® applied. The blotting paper with the adherent specimen is then placed in a fixing agent and sent to the pathologist. Such material should be given priority in any pathologist's practice, and the examination should be made promptly and the result reported in order to facilitate early and correct treatment.

A nonulcerated lesion should be excised *in toto* with a narrow margin of normal skin. This can be done under local anesthesia without discomfort to the patient. Under no circumstance should the electrocautery or fulgurating needle be used without first securing a histologic diagnosis. The use of the cautery loop for biopsy often coagulates the specimen beyond recognition. Bleeding has never been difficult to control in my experience. Pressure or, at most, a single suture will suffice.

It is wise not to discuss the diagnosis with the patient on clinical grounds alone, since a perfectly benign lesion may often be mistaken for a malignant one and radical therapy advised. For example, a pyogenic granuloma may commonly be mistaken for a malignant melanoma or other form of skin cancer. This lesion fungates and bleeds freely on slightest

trauma, recurs promptly after local measures, and may give the impression of a highly malignant tumor which requires amputation of a digit or even wide surgical excision. However, once the true nature of a pyogenic granulomatous lesion is disclosed by biopsy, treatment requires only a relatively small dose of contact radiation (800 r through an appropriate portal at contact distance with a 44 kv. Phillips tube). The reverse is also true; an apparently benign lesion may, on histologic examination, prove to be a highly malignant tumor requiring radical surgery for its eradication. A malignant melanoma is a notorious example, since it may appear relatively benign on clinical examination.

In compiling the history and making the examination, it is always interesting to note the occupation and the complexion of the patient. In my experience, patients with blond sandy hair, fair complexion, and a tendency to freckle are more susceptible to the development of epitheliomas and melanomas of the skin than brunettes or patients with a complexion that tans rather than burns. Fishermen, sailors and sun bathers have a high incidence of skin cancers on exposed surfaces. Persons who are exposed to tar, pitch, oils, paraffin and nitrates have been known to have skin cancers as a direct result of such exposure. The administration of arsenicals over a long period of time leads to an arsenical keratosis which, in turn, develops into squamous carcinoma even in the unexposed portion of the skin. Examination of the palms of the hands will often give a clue to such a history, as the arsenical palm is dry and thickened. The evidences of previous roentgen exposure in cases of multiple telangiectasia and keratosis will often suggest the reason for the ulcerating lesion that is present.

As has been pointed out already, the value of polydiagnosis both in prophylaxis and treatment of malignant skin lesions cannot be overemphasized. It is not unusual to encounter a patient with a skin cancer or even early malignant melanoma which has been completely ignored while the patient is being treated for some less important symptom or pathologic condition.

***Treatment***

Once the diagnosis has been established by proper history, physical examination and biopsy, certain general principles of treatment can be followed. After reviewing 1500 case histories, it is my opinion that malignant melanoma requires radical surgical therapy; roentgen ray, radium, electrocautery and escharotics have been abandoned as useless in treating patients with this disease. Fortunately, malignant melanoma is rare, though this very rarity is often the cause of improper diagnosis and treatment, leading to the disastrous results and hopeless prognosis which are associated with it.

In cases of malignant melanoma, ulceration increases the gravity of the prognosis, as does the occurrence of the disease in the mucous membrane or at the mucocutaneous junction. Lesions occurring on the genitalia or those which are activated during pregnancy are associated with a high mortality rate as a result of widespread metastasis. The nonulcerated lesion that has been excised with a narrow margin requires re-excision of the surrounding skin for a distance of at least 6 cm. on all sides, and closure with a skin graft. If the lesion is situated within a reasonable distance of one of the node-bearing areas, a block dissection of the tumor, subcutaneous fat, fascia and lymph nodes of the entire drainage area should be done in continuity. It is interesting to note that about 20 per cent of patients without palpable nodes will be found to have metastatic disease at the time of the initial dissection.

Subungual melanoma should be treated by amputating the digit involved. If enlarged nodes are present at the time of discovery of a lesion on the distal part of an extremity, the extremity together with the lymphatic drainage area should be removed. Interscapulothoracic amputation with excision of the axilla should be performed if the upper extremity is involved, and hip-joint disarticulation or hemipelvectomy with deep dissection of the iliac nodes should be performed if the lower extremity is involved. If no palpable nodes are present, the patient is observed carefully at two month intervals during the first year,

at three month intervals during the second year, and so on until five years have elapsed, and then at six month intervals for the rest of his life. The vast majority of melanomas will recur within 18 months if the initial treatment has not been adequate, though I have seen recurrence as long as 17 years later. It is the duty of the general practitioner to insist that an adequate operation be performed. It is my feeling that the dermatologist and the radiologist should not treat the patient with malignant melanoma.

The patient with epithelioma, in general, can be treated either surgically or radiologically with equally good results, provided adequate surgery is performed and adequate radiation is administered. Operation is best employed for lesions on the hand and over bony prominences. A margin of normal tissue of at least 1.5 to 2 cm. should be excised with the lesion, and the defect closed with a split thickness graft or appropriate pedicle flaps. A discontinuous dissection of the subtending node-bearing area is permissible provided both the primary lesion and the metastatic involvement of the lymph nodes are not present at the same time. If both are present on initial examination, dissection in continuity or amputation and node dissection should be done.

Radiation therapy, if given carefully, yields excellent results. It must be noted, however, that the dose required to permanently destroy an epithelioma is very close to that which will produce radionecrosis of the normal skin. Fractional dosage, careful shielding of the surrounding skin, and physical control of the apparatus used are of utmost importance. Radium needles and plaques of standard measurement and dosage can be used to advantage in the treatment of skin cancer in that the cosmetic result is better because of the less sharply demarcated reaction. Metastatic squamous cancer in lymph nodes is rarely curable by the use of x-ray therapy supplemented by the interstitial use of radium or radon, and had best be left to the care of the surgeon. The use of escharotics in treating skin cancer was abandoned by Celsus shortly after the time of Christ and has no place in the scientific treatment of cancer today.

Paget's disease, when involving the nipple, requires radical mastectomy. Extramammary Paget's disease is preferably treated surgically, though radium and roentgen treatment have proved efficacious. Bowen's disease is better treated surgically, though radiation with x-rays or radium might be tried first, and surgical treatment used subsequently in cases in which radiation therapy is not effective, as in cases of epithelioma. Sarcomas of the skin such as dermatofibrosarcoma and neurogenic sarcoma require wide surgical excision. Kaposi's sarcoma and the lymphoblastomas should be treated by the radiotherapist.

The precancerous dermatoses are best treated by preventive measures such as avoiding overexposure to radiant energy, whether it be sunlight or x-rays. The prompt grafting of second-degree burns, protection of skin in occupational hazards, and appropriate treatment of chronic ulcers will prevent the formation of epitheliomas that are notoriously difficult to cure. Once the precancerous lesion has occurred, it is probably best to use surgical measures for its eradication, since the x-ray or radium dosage necessary to destroy these lesions is usually of sufficient magnitude to produce a radiodermatitis which, in itself, is subject to epitheliomatous degeneration at a later date.

# The Diagnosis of Cancer of the Head and Neck

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THE prognosis of cancer of the head and neck is favorable when compared with the prognosis of malignant neoplasms arising in the stomach, intestines, lungs, kidneys and other deep-lying structures. This is quite understandable when one considers that 80 per cent of these tumors are evident to the patient and the physician at an early stage in their growth. It is, however, somewhat more difficult to understand why the prognosis is not better.

The culpability rests with both the patient and the physician.[1] The average individual mirrors himself at least once daily in performing his tasks of cleanliness but is prone to ignore any nonhealing lesion of the skin, lips, tongue, palate or gingivae which is not accompanied by pain. On the other hand, the physician, too, is prone to minimize a small growth of the oral cavity, an ulcer of the skin of the face, or a lump in the neck when it is an incidental finding in a case in which the patient is being treated for another disease. However, the mere fact that the physician glanced at the lesion and did nothing specific about it gives the patient the false assurance that it is nothing about which to be concerned. Any lesion which is noticed on routine examination and which is not very obviously benign should be investigated.

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### *Cancer of the Skin*

Malignant lesions of the skin of the head and neck are perhaps the most obvious to both the patient and the physician. The most common of these is basal cell carcinoma which usually occurs as a small, dry, crusted ulcer or nodule with raised margins which give it an umbilicated appearance. As the crust is removed, the lesion bleeds easily, and induration can be felt along its margins. The history is one of slow growth over a period of several years. For this reason, these lesions may be confused with chronic ulcers of the skin.

In contrast to basal cell carcinoma is squamous cell carcinoma which is characterized by a granulomatous ulcer with induration around its margins. This lesion occurs far less frequently than basal cell carcinoma; it usually grows rapidly and is prone to metastasize to the regional lymph nodes. In addition to these two types of lesions, one should also be suspicious of an apparently benign nevus accompanied by a darkening in pigmentation, an increase in size, or ulceration and bleeding. These, of course, are changes characteristic of malignant melanoma.

### *Cancer of the Oropharyngeal Cavity*

The oral cavity lends itself well to adequate physical examination. The complete oral examination should begin with inspection and

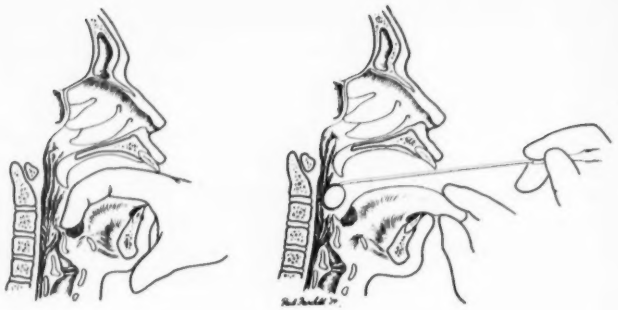

FIGURE 1. Examination of the base of the tongue. The palpating finger and laryngeal mirror are indispensable for examination of the base of the tongue and the vallecula. It is possible to overlook a sizable lesion in this region when examination is performed only with a tongue blade and a flashlight.

palpation of the entire cavity, which should be started at the gingivobuccal gutters and extended to the gingivae and the floor of the mouth. The tongue should be deviated first to one side and then to the other by the aid of the tongue blade in order to visualize the junction of the base of the tongue with the floor of the mouth. Having the patient say "ah" depresses the tongue, raises the soft palate, and enables one to obtain a better view of the pharyngeal cavity. This, however, should not end the inspection. It is not possible with an ordinary tongue blade and flashlight to visualize the base of the tongue, the vallecula, the epiglottis and the larynx; and it should be emphasized that this is a very inadequate method for thorough examination of this area.

The laryngeal mirror is indispensable in examining this portion of the oropharyngeal cavity. Occasionally, it is necessary to anesthetize the mucosa before the patient will tolerate this type of examination. No examination of the oropharyngeal cavity should be considered without the use of the laryngeal mirror. Equally as important as inspection is palpation. The rubber-gloved or cotted finger is an invaluable means of palpating the base of the tongue, and it also provides a good means of leverage for manipulating the tongue and for examining the floor of the mouth. This examination can extend as far as the vallecula (figure 1).

The most common type of carcinoma of the oropharyngeal cavity is squamous cell carcinoma. This usually appears as a small, nontender, ulcerated, granulomatous lesion with raised margins surrounded by a definite area of submucosal induration. This lesion may appear anywhere in the oral cavity. The patient will often confuse this with a canker sore. The basic differential point, however, is that a canker sore usually is painful while an early malignant lesion usually is painless. This may also be considered in regard to the differential diagnosis of other oral lesions such as stomatitis, glossitis and traumatic lesions. As the malignant lesion enlarges, and especially as it becomes secondarily infected, the patient will experience pain. If the neoplasm should involve the larynx or pharynx, hoarseness, dyspnea and some degree of dysphagia usually are present. If the patient complains of vague and rather indefinite symptoms referable to the pharynx or larynx, and if digital examination and examination with a laryngeal mirror do not result in a definite diagnosis, direct laryngoscopy and roentgenologic examination should be performed.

The neoplasm of the head and neck that accounts for most deaths is cancer of the tongue.[2] In the past, this lesion has been confused with a syphilitic gumma, and it has been rather common teaching that a serologic test for syphilis should be performed before treatment of an ulcerated, granulomatous lesion of the tongue is started. It has since been found that the results of a serologic test for syphilis are positive in a rather high percentage of cases of cancer of the tongue. The results of this test have been positive in as many as 33 per cent of some series of cases of cancer of the tongue.[3] In cases of this type of lesion, antisyphilitic therapy should not be instituted solely on the basis of a positive result of a serologic test for syphilis. A positive result of

such a test is no contraindication for biopsy. *Any oral lesion which has persisted longer than two weeks with progression rather than regression in size should be considered neoplastic and is an indication for biopsy.*

Biopsy of such a lesion is a simple procedure and can be carried out in the physician's office. One may use the usual biting forceps, an ordinary scalpel blade, or a punch biopsy instrument. A small amount of infiltrating anesthesia is often necessary; however, a biopsy can be performed frequently without this. The specimen should include a small portion of the base and the margin of the lesion as well as a small amount of adjacent normal tissue. The amount of tissue removed should be small enough not to require suturing of the wound. A mild degree of pressure should be sufficient to stop any bleeding, or the area may be cauterized with a silver nitrate stick. The final diagnosis *must* be made by microscopic examination, and treatment should *never* be instituted until the pathologic nature of the lesion is known.

### *Cancer of the Neck*

The examining physician must realize that lumps in the neck may be of three types: (1) congenital (such as cysts, fistulas and solid cell rests), (2) inflammatory (such as nonspecific cervical adenitis, tuberculous adenitis or sialitis), or (3) neoplastic. The neoplastic lesion in turn may be primary or metastatic. The most common primary malignant lesions which occur in the midline of the neck are those referable to the thyroid gland and to the larynx. Primary malignant tumors off the midline are not very common; but branchiogenic carcinoma, a malignant carotid body tumor, a salivary gland carcinoma, or even the more rare malignant tumors which originate in muscle, nerve and fatty tissue occur occasionally. However, the unilateral mass in the neck is most often the result of an oral or pharyngeal cancer which has metastasized to the cervical lymph nodes in this area.

### *Metastatic Cancer of Lymph Nodes*

The most important chain of lymph nodes involved by a cancer originating in the oropharynx is that which extends along the deep jugular chain, but the submaxillary, submental and spinal accessory chains may be involved. A primary lesion anywhere in the oropharyngeal cavity may involve any of these nodes; however, cancer of certain parts of the oral and pharyngeal cavities seems to have at least an early predilection for certain parts of the lymphatic chains just described. For instance, carcinoma of the lip will, in a great percentage of cases, involve the submental nodes first. Carcinoma of the base of the tongue will usually metastasize to the upper or midjugular chain as its first line of spread, whereas carcinoma of the nasopharynx will usually metastasize along the posterior accessory chain. Carcinoma of the thyroid, on the other hand, usually will spread along the transverse cervical chain (figure 2).

An involved node in the neck typically feels

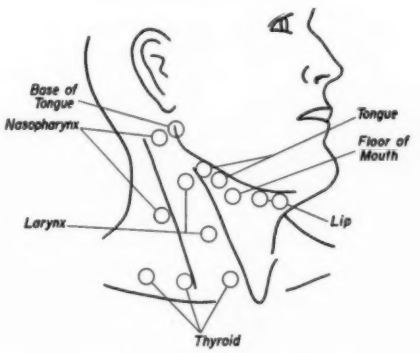


FIGURE 2. Diagram showing the usual route of metastasis of a primary cancer of the oropharyngeal cavity to the cervical lymph nodes. Primary cancer of the oropharyngeal cavity or neck may involve any lymph node.

firm. It may be fixed or movable depending on the extent of the involvement, and it usually is not tender as it is in cases of inflammatory lesions. There is most often a history of progression in the size of the mass. If a patient has a swelling in the neck, and if any or all of these symptoms or findings are present, he should *first* be subjected to a thorough physical examination. A careful history should be taken, for this will often indicate the diagnosis

of a benign, congenital or inflammatory lesion. For example, tender swollen nodes in the upper jugular chain of a child with tonsillitis would probably be caused by adenitis. An asymmetric, firm, nodal enlargement in an adult should *always* be considered malignant unless proved otherwise. Careful, thorough investigation of the oropharyngeal cavity should be carried out in the search for a primary lesion.

The removal of a lymph node for biopsy is not only *unnecessary*, but may prove to be harmful and even account for the difference between salvage and death for a particular patient. When a node is removed, lymphatic channels are opened and the possibility of contamination of surrounding tissue with tumor cells is present. In addition, as a result of the surgical procedure, scarring takes place so that it is not possible to adequately resect the lesion if this becomes the treatment of choice. Deaths have been caused by damage of the carotid artery resulting from subsequent dissection in the vicinity of that vessel after an adjacent lymph node has been removed.

Aspiration biopsy is the procedure of *choice* in establishing a diagnosis. In many cases this will reveal the presence of fluid, indicating a cystic lesion. Aspiration biopsy is a rather simple procedure to perform.[4] By using local anesthesia, a 16 or 18 gauge needle with a stylet is first introduced through a small opening in the skin and into the tumor proper. The stylet is then removed, and a 30 cc. or 50 cc. syringe is attached. The plunger is withdrawn to create suction, and the needle is rotated as well as introduced to-and-fro through the substance of the tumor to obtain tissue in the lumen of the needle. The suction is then released, and the needle is withdrawn. The contents of the needle are first smeared on slides. However, an actual core of tissue can often be removed, and it is placed on a small bit of blotter paper which can be introduced in Formalin for preparing permanent sections. Usually, enough tissue can be obtained in this manner to provide sections as good as would be obtained when biopsy is performed in the usual manner (figure 3).

The diagnosis of metastatic carcinoma of the lymph nodes is not difficult to make whether or not a definite primary carcinoma is known to exist. If the pathologist who is familiar with the cytologic appearance of cancer cells finds anaplastic epithelial cells in a lymph node, a diagnosis of metastatic carcinoma can be made. If a definite diagnosis cannot be made by aspiration biopsy, a specimen should be obtained by formal biopsy. It is advisable that the specimen be obtained in the operating room. Frozen section should be made, and if a diagnosis of carcinoma is made, the surgeon should proceed immediately with the surgical resection.

FIGURE 3. Core of tissue that often can be obtained by aspiration biopsy. Such tissue either can be smeared on slides for immediate fixing and staining or can be placed in FORMALIN® and handled as specimens obtained in the usual manner.

### *Conclusions*

As a general rule, it may be stated that any nonhealing lesion of the skin or oropharyngeal cavity and any mass in the neck *must* be considered malignant until proved otherwise. Biopsy should be performed early in the course of its growth to establish a diagnosis and permit early treatment. Only in this manner will a greater number of patients with cancer of the head and neck be salvaged.

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# Neoplasms of the Colon

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CANCER of the colon is common. This organ is the site of 7 per cent of all malignant neoplasms affecting the human body; it is host to 95 per cent of all tumors involving the intestinal tract;[1] and from 30,000 to 35,000 American people die annually from cancer of the colon and rectum.[2,3]

The past three decades have brought forth many improvements in methods of dealing with cancer of the colon and, at present, if the condition is diagnosed early and treated by appropriate surgical operation, it offers better opportunity for cure than any other type of internal malignant growth. There still is need, however, for continued effort to improve further the rate of salvage in these cases. Fansler[4] has stated that any extension of the surgical attack on cancer of the colon will improve but little the present salvage statistics. Greater emphasis must be applied to early diagnosis of cancer of the colon and its precursory lesions. It seems fitting, therefore, to present a brief clinic stressing the objective approach in diagnosis of colonic neoplasms.

CHARLES W. MAYO

DONALD R. DAVIS

### *Investigation of Symptoms*

The symptomatology of cancer of the colon is vague. There are no symptoms, nor is there a group of symptoms, that can be designated as pathognomonic for early malignant disease of the colon. The examining physician must be sensitized to the possibility of colonic can-

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cer when any patient presents himself with gastrointestinal complaints, no matter how vague they may be. A concept of the mechanisms whereby cancer of the colon produces its symptoms affords a valuable adjunct to the physician's inquisition.

Early, uncomplicated cancer of the colon is, in fact, asymptomatic save for occasional minor digestive disturbances to which the patient attaches little or no significance. Symptoms are not apparent until the disease is well established, and their expression is usually the result of one or more of the various complications to which the tumors may be subjected or which they may cause; namely, ulceration, secondary infection, obstruction, perforation and fistula.

A form of pain is the most common presenting symptom, irrespective of whether the tumor occupies the right or the left portion of the colon. It is usually intermittent and is cramping in nature. Often it is a dull ache, occurring without reference to bowel action or the taking of food and, in either case, it is attributed to varying degrees of intestinal obstruction, local inflammation, peritoneal invasion or extension of the tumor to surrounding structures. All cancers of the colon are eventually complicated by ulceration and infection, regardless of their histologic types, and this is probably responsible for the earliest symptoms in most cases. At their onset, these symptoms are not severe enough to send the patient for medical advice. As ulceration progresses, however, changes in bowel habit supervene with increasing severity, and vary from mild looseness of the stool or constipation to full-blown diarrhea or stubborn obstipation. Fluid stools are more common with right colonic lesions whereas left colonic cancers have a greater tendency to cause constipation. The ulcerated surface has a tendency to bleed and, depending on the amount of bleeding and site of the tumor, produces characteristic changes in the stool. Mucus may appear as the result of inflammation of the mucosa adjacent to the tumor or as a product of a mucus-producing cancer.

Twenty-five per cent of all intestinal obstructions are of the large bowel and 85 per cent of these are due to carcinoma. Left colonic lesions will obstruct with eight times the frequency of right colonic lesions because the diameter of the bowel is smaller, the contents of the fecal stream are more solid, and lesions of the left portion of the colon have a tendency to spread laterally on the mucosal surface and to encompass the entire bowel. Obstruction may occur from the tumor's filling the lumen, associated fibrosis such as occurs with scirrhous carcinoma, angulation of the bowel, inflammation, edema, volvulus or intussusception. Perforation, abscess and fistulas are late sequelae of obstruction.

Toxemia or anemia or both are frequent accompaniments of large ulcerating lesions of the right portion of the colon and may be the only symptoms. Why anemia should occur so frequently has occasioned much conjecture, and many theories have been advanced to explain it. The most plausible explanation seems to be that it results from a combination of absorption of noxious substances, such as bacterial toxins and proteins with hemolytic properties, and insidious but direct loss of blood from the ulcerated area.

The right and left halves of the colon differ so markedly in embryologic development, anatomy and function, and the manifestations of disease affecting the right and left halves are so distinct, that one is inclined to think of each half as a separate and distinct organ. The right colon, of midgut origin, is of fairly large caliber; its contents are liquid and its function is largely absorption. The hindgut gives rise to the left colon and its diameter is small; its contents are more or less solid, and its function is storage. Comparatively little absorption takes place in the left half of the colon. These factors explain, in part at least, why right and left colonic tumors differ in their clinical manifestations.

*The system review*—Regardless of the presenting complaint, diagnostic study of every patient should entail a definite routine, embodying a group of direct questions referable to the state of health, or absence of health, of the intestinal tract. Seemingly insignificant details may denote serious disease and the need for special study. As an example, con-

sider the following hypothetical case:

A 42 year old farmer's wife, the mother of a large family, presents herself to the physician to determine whether she suffers from peptic ulcer. She has had occasional bouts of abdominal distress between meals and at night for two months and has received partial relief from the taking of food. Her husband, an ulcer patient, noticed the similarity between her symptoms and his own and referred her for treatment.

In the course of her routine work-up, the patient was interrogated in part as follows:

PHYSICIAN: Aside from the pain that you complain of, do you feel entirely well in every other respect?

PATIENT: Well, Doctor, I have noticed that I tire rather easily. I don't seem to have the usual amount of "pep."

PHYSICIAN: Have you had any fever that you are unable to explain?

PATIENT: No, Doctor.

PHYSICIAN: Has your weight changed within the past six months?

PATIENT: Yes, I have lost about nine pounds.

PHYSICIAN: Why? Have you been taking a diet for the purpose of losing weight?

PATIENT: No, Doctor, I have been eating my normal diet and my appetite has been about average. I have been working rather hard at home lately, however, and that may be the reason for my weight loss.

These symptoms could accompany peptic ulcer. Fatigability and loss of weight are not usually prominent in this condition, however; they often are the only symptoms of cancer of the right portion of the colon. To continue the questioning:

PHYSICIAN: Have you experienced any other symptoms referable to your abdomen, such as an unusual amount of gurgling, crampy pain, aches or flatulence?

PATIENT: Yes, Doctor, now that you mention it, I have noticed more noises in my abdomen than usual and occasionally they are accompanied by slight cramps. I thought it was just "gas." What do you mean by "flatulence," Doctor?

PHYSICIAN: By that I mean a feeling of abdominal fullness, such as would occur from an excessive amount of gas in the stomach or intestines. Have you found that your girdle fits more snugly than usual, or perhaps a belt you have been wearing seems tight?

PATIENT: No.

These questions are designed to uncover any symptoms of low-grade intestinal obstruction, such as might occur with a neoplasm of the colon. When answered in the affirmative they must be considered to carry great significance, particularly when they are attended by other supporting symptoms or signs. To stress the use of language familiar to the patient may seem redundant; nevertheless, it is very important in the securing of an accurate history.

PHYSICIAN: Has the nature of your bowel action changed in any manner during the past year?

PATIENT: No, Doctor.

PHYSICIAN: Are you certain? Have you had any minor bouts of diarrhea or constipation? Have you noticed any blood in your stools, or have the stools appeared darker than normal at any time?

PATIENT: Now that I think about it, I did have a couple of loose stools about two weeks ago and about three weeks before that I had some diarrhea that lasted two and a half days. I did not pay much attention to it because it subsided promptly when I took some paregoric I had for the children. My stools are normal now.

PHYSICIAN (repeating): Have you noticed any blood in your stools? Have they been excessively dark?

PATIENT: No.

Inquiry as regards the bowel habit is, of course, important and must be complete. Every question must be answered to the physician's satisfaction. Persistence in questioning may spell the difference between diagnosing an early lesion and missing it. When the patient gives a history of bloody or dark-colored stools one should determine whether iron or "other medicine for the blood" has been taken by the patient, whether it was a mere streaking of the paper with bright blood or whether blood was actually on the stool or mixed with it. A melenic stool is malodorous.

PHYSICIAN: Have you noticed any lumps or masses in your abdomen?

PATIENT: No.

It should be stressed that the accidental discovery, by the patient, of a mass in the abdomen often is the only presenting sign of cancer of the right portion of the colon.

PHYSICIAN: Have you had any abdominal operations in the past?

PATIENT: Yes, I had my appendix removed at the age of 10.

PHYSICIAN: Was your appendix ruptured?

PATIENT: Yes.

It is important to determine whether a background for intra-abdominal adhesions exists in view of the fact that they are the commonest cause of intestinal obstruction.

Further review of the patient's systems should include questions relative to the gallbladder and appendix, inasmuch as carcinoma of the right portion of the colon has been known to mimic acute and subacute inflammation of these organs. A patient with diverticulosis usually will give a history of repeated attacks of symptoms similar to those of appendicitis but situated in the left lower part of the abdomen. Review of the urinary system may bring out symptoms of ureteral inflammation or obstruction or, perhaps, of involvement of the bladder itself. Needless to state, pneumaturia and fecaluria, such as occur with vesicocolonic fistula, hardly can be considered early symptoms of carcinoma of the colon.

Like a jigsaw puzzle, the pieces now begin to form a picture. Here is a woman, 42 years of age, which is well within the cancer age, thorough and persistent questioning of whom has brought forth a history suggestive of a malignant lesion involving the right portion of the colon. Rankin, Bargen and Buie[5] have placed the symptoms of right colonic lesions in three general groups: (1) the dyspeptic group (60 per cent) in which the symptoms are mild and there are few localizing signs, (2) the anemic group (30 per cent) characterized by fatigability and loss of strength and weight, and (3) the group characterized by accidental discovery of a mass in the abdomen (10 per cent).

This imaginary patient has the commonest symptom of colonic neoplasm, which is pain, although admittedly the pain is somewhat bizarre. In addition, close questioning has brought forth a history of dyspepsia, of change in bowel habit and, finally, of symptoms suggestive of anemia. It is known that cancer of the right half of the colon, accompanied by inflammation, is capable of mimicking duodenal ulcer by virtue of the close approximation of the cancer to the retroperitoneal portion of the duodenum with resulting duodenitis. This hypothetical case illustrates this phenomenon.

### *Examination of the Patient*

Physical examination should include careful inspection of the abdomen for evidence of peristaltic rushes, abdominal scars or a region of visible fullness suggesting the presence of a mass. The gallbladder and appendiceal regions should be palpated, and an effort should be made to feel the liver for enlargement or nodularities. Percussion will give information relative to the possibility of undue intestinal gas, and one should listen for the high-pitched, tinkling borborygmi characteristic of intestinal obstruction. Certainly, the anus and rectum of every patient should be examined digitally, and all female patients should undergo bimanual pelvic palpation.

*Special studies*—Now, with reference to diagnostic studies, how shall the investigation proceed in a case in which symptoms are referable to the lower part of the intestinal tract? In the imaginary case with which this clinic is concerned, it was necessary to prove or disprove the presence of a right colonic neoplasm, or of a duodenal ulcer. In such a case, the lower part of the bowel must be investigated first, and oral administration of a suspension of barium strictly avoided until such time as it has been proved that an obstructing lesion does not exist in the lower portion of the intestinal canal.

It is best to commence with proctosigmoidoscopic examination. The next step should be a barium enema study, in which the ascent of the column of barium is inspected under the fluoroscope and representative spot films

are taken of any portions which arouse suspicion. Following evacuation of the barium, the colon is insufflated with air for double-contrast studies. Hesitancy need not be felt about repeating an x-ray study of which the results are equivocal. Even if the second study gives a negative result, the patient should be advised to return for another study if his symptoms persist. Investigation of the upper part of the gastrointestinal tract should be deferred, as was stated earlier, until the absence of an obstructive lesion is demonstrated.

Although a carefully taken history is recognized as the most important item in the early diagnosis of colonic malignancy, the actual proof of the presence of this condition lies in the hands of the radiologist when the lesion is above the reach of the sigmoidoscope. If the patient is actually harboring a malignant growth, the combination of proctosigmoidoscopic examination and barium enema study, which is followed by double-contrast studies, will give direct or indirect evidence of presence of the lesion in nearly 100 per cent of cases. Radiologists with whom we work on numerous occasions have visualized polyps the greatest diameter of which at exploration proved to be no more than 3 or 4 mm.

### *The Precursory Lesions*

The basic objective is to reduce the mortality rate from cancer of the colon. This clinic, therefore, must deal with the prevention of cancer. Approximately 12 per cent of all persons harbor potentially malignant lesions in their colons or rectums at some time in their lives.[6] It is necessary to discover and eradicate such lesions, particularly adenomatous polyps, the lesions of familial polyposis and those of chronic ulcerative colitis.

*The adenomatous polyp*—Adenomatous polyps of the rectum and colon are among the most dangerous precursors of cancer[7,8] and, furthermore, the most common. Hitchcock and Aust[6] reviewed the records of 5,352 men and women examined at the Cancer Detection Center of the University of Minnesota between March 1948 and February 1953. They found that 1.7 per cent of these people had clinical cancer and that the colon or rectum was the primary site with twice the frequency of any other organ. Thirteen hundred, or 24 per cent of their total group, had precancerous lesions of one kind or another, 624 of which, or approximately half, were adenomas of the rectum and colon. This is an incidence of 11.6 per cent of all persons examined. It can be presumed that, if given sufficient time, clinical carcinoma of the rectum or colon would develop in all of them and a certain portion of them would die of their disease.

Hauch, Buie, Bargen and Smith[2] studied results of a series of 1,919 routine proctosigmoidoscopic examinations of patients who had no symptoms referable to the gastrointestinal tract, and they found that 8.1 per cent had polyps in their rectums or the sigmoid portion of their colons. In view of these facts, it is obvious that the "polyp-conscious doctor" can render great service to his patients by detecting and treating these lesions in the early stages of their development. He should remember that 1 of every 10 persons more than 40 years of age will have polyps which can be seen on proctosigmoidoscopic examination.

Once a polyp has been discovered, its immediate removal is essential to the safety of the patient. The size of the growth gives no indication as to the presence or absence of malignancy, nor can it be predicted when a given polyp will undergo carcinomatous change. Once a polyp has been destroyed, by either fulguration or surgical means, the patient should be instructed to watch carefully for signs of rectal bleeding and to be examined frequently for recurrence. At the Mayo Clinic we see these patients at intervals of six months for the first year and, if no further polyps are found, annually thereafter. The incidence with which more polyps develop in these patients is remarkably high. Buie[9] found that in 21 per cent of cases more polyps will develop after fulguration of polyps in the rectum, and Judd and Carlisle[10] have shown that in 28 per cent other polyps will develop after transcolonic excision. Hence, the necessity for follow-up is apparent.

In medical schools, hospitals and teaching clinics, students should be urged to familiarize themselves with the use of proctoscopic

equipment and to learn the value of adequate examination of the rectum and terminal portion of the colon. General practitioners not fully acquainted with the technic of proctosigmoidoscopic examination should take time off from their busy practices to observe and learn the procedure, that they might make this relatively simple study available to their patients. Such an examination can be performed in the office without anesthesia, since it is relatively painless. We urge that every patient who is undergoing annual routine examination, and who is 40 years old or more, submit to proctosigmoidoscopy and perhaps to roentgenologic examination of his colon.

*Familial polyposis of the colon*—People with familial polyposis almost invariably die of carcinoma of the colon or rectum if they are not treated and if they live long enough. It is estimated that approximately 50 per cent of persons with familial polyposis will be dead of cancer by the age of 30,[11] whereas practically all of them will have advanced abdominal cancer, or will be dead of cancer, by the age of 50 years.[8] In the experience of one of us (C. W. M.), only one patient has come to total colectomy for polyposis who was more than 50 years of age and who did not have advanced carcinoma of the colon. This patient was a man 51 years old.

Total colectomy is the only safe and acceptable treatment for this disease in view of its malignant potentialities. This view is universally accepted. Follow-up examination of the rectum in the years after operation is extremely important, and its necessity must be stressed with emphasis to the patient. All patients will have further polyps which will require fulguration. Black and Hansbro[12] found that, of 26 patients, all but one had rectal polyps which required fulguration each year for four years after operation. It is to be remembered that treatment of this condition by total colectomy and ileorectostomy will be successful only if the polyp-bearing rectum is examined periodically for as long as the patient may live.

*Chronic ulcerative colitis*—Bargen, Sauer, Sloan and Gage[13] recently reported their results of a study of 1,564 cases of chronic ulcerative colitis in which they attempted to determine the frequency with which carcinoma develops among people who have this disease. They found that 6.3 per cent of their group died of cancer of the colon. Not concerning themselves with patients in whom cancer might develop later, they compared the number of observed cancer deaths in their group with the expected number of deaths from cancer of the colon in the general population, utilizing the death rates supplied by the United States Bureau of Vital Statistics. They concluded that among people with chronic ulcerative colitis, cancer of the colon and rectum develops 30 times more frequently than among individuals of similar age groups in the general population. It has been noted that, as compared with those attacked later in life, the incidence of malignancy is greater among persons afflicted with chronic ulcerative colitis at an early age,[14] that the grade of malignancy is usually of a high order,[15] that the cancers frequently are multiple (14 per cent),[14] and that the outlook for these patients is usually grave.[15]

The physician should observe these patients carefully for polypoid change, and for any change in symptoms suggestive of clinical cancer. Opinion is widely divided as to the proper method of dealing with this disease. Some advocate total colectomy, with establishment of a permanent ileac stoma in every case as soon as the diagnosis has been established. Others adhere to a more conservative view, resorting to surgical intervention only in the event of definite secondary indications such as intractability, hemorrhage, stricture, polypoid change and malignant degeneration. We, at the Mayo Clinic, have been somewhat conservative in treatment of this disease but we feel that periodically all patients should be examined, their histories reviewed, appropriate laboratory studies made and their colons inspected proctoscopically and roentgenologically, in order to detect any evidence of supervening malignant metaplasia at the earliest possible moment.

If polyps complicate chronic ulcerative colitis, those within reach of the sigmoidoscope should be fulgurated, preferably in the course

of a remission, to avoid flare-up of the disease if possible, and polyps above sigmoidoscopic levels should be examined frequently by fluoroscopy and roentgenography to detect any change in size. Should a polyp show change on successive examinations, malignant change must be considered seriously and total colectomy performed.


### *Summary*

Cancer of the colon is common. It accounts for 7 per cent of all neoplasms affecting the human body. The symptomatology of cancer of the colon is vague. The physician must be sensitized to the possible presence of colonic cancer when he questions any patient who complains of gastrointestinal symptoms. Tumors of the right and left halves of the colon differ in their clinical manifestations. This is explained on the basis of the different embryonal development, anatomy and function of these portions of the colon.

Every patient who is undergoing diagnostic study should be questioned with special reference to the state of health, or absence of health, of the intestinal tract. Special studies of the gastrointestinal tract should commence with proctosigmoidoscopic examinations. These should be followed by barium enema with fluoroscopy, plus spot films of areas under suspicion, and these by double-contrast roentgenographic studies. Oral administration of barium should be avoided until it has been proved that an obstructing lesion does not exist in the lower intestinal tract.

Every patient more than the age of 40 years who undergoes routine physical examination should submit to proctosigmoidoscopic examination and roentgenologic inspection of his colon. Twelve per cent of all persons harbor lesions of malignant potentialities in their rectums and colons at some time in their lives. Adenomatous polyps of the rectum and colon are among the most dangerous precursors of cancer and, furthermore, the most common. One of every 10 persons more than 40 years of age has one or more polyps discoverable by proctosigmoidoscopic examination. People with familial polyposis invariably die of carcinoma of the colon if they are not treated and if they live long enough. Among people with chronic ulcerative colitis, cancer of the colon and rectum develops 30 times more frequently than among individuals of similar age groups in the general population.


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# Diagnosis of Tumors of the Urinary Tract and Male Genital System

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TUMORS of the urinary tract and of the male genital system are usually detected by a complete history, a thorough physical examination and special diagnostic procedures indicated in each individual case.

### *Renal Tumors*

Renal embryoma, or Wilms' tumor, occurs in early childhood. Tumors of the adult kidney usually occur after the fourth decade of life. Wilms' tumors are rarely recognized until sufficiently large to be palpated. They are usually discovered by the mother or nurse while bathing the child, or by the physician during a routine physical examination. These tumors rarely bleed. They may be confused with tumors arising from the retroperitoneal area consisting of sympathetic nerve tissue or of lymphatic origin.

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A pyelogram usually will show that the renal pelvis is distorted and misplaced, and it may reveal that the ureter has been pushed from its normal course (figure 1). It also will distinguish a renal tumor from cystic disease or congenital hydronephrosis.

The presence of a malignant tumor of the adult kidney usually is suspected when hematuria occurs, when pain is present in the lumbar region or in the upper part of the abdomen, or when a mass is present in the renal region. Barrett and McCague made a study of 157 patients with malignant tumors of the kidney and found that 105 had hematuria, 103 had pain and 55 complained of the presence of a tumor. Less common presenting symptoms are fever, loss of weight and anorexia.

Malignant tumors also occur in the renal pelvis, and in many instances they invade the renal parenchyma. Papillary tumors may cause rather profuse bleeding. As in cases of tumors

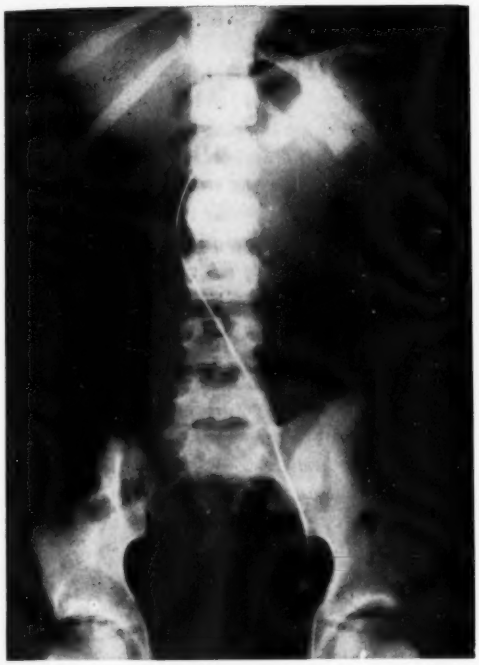

FIGURE 1. Left renal pelvis elevated and ureter pushed past midline of abdomen by Wilms' tumor of lower pole of kidney.

of the parenchyma, the bleeding is usually spontaneous and frequently disappears for long periods. Renal colic may result from blood clots occluding the ureter, and the kidney may become enlarged because of an obstruction at the ureteropelvic orifice.

The infiltrating tumors of the renal pelvis do not often cause profuse bleeding. Microscopic hematuria usually is present, and pyuria is frequent. The unfortunate patients may be treated for chronic pyelonephritis until the disease is inoperable.

The patient most frequently consults the physician because of blood in the urine, pain in the lumbar region or upper part of the abdomen, or because of the discovery of a mass. By careful palpation with the patient well relaxed, the least suggestion of fullness in the area beneath the twelfth rib can often be noted when the tumor has not been recognized by the patient. Pain results from tension within the tumor, from pressure on the ureter when the mass is at the lower pole of the kidney, or from blood clots partly occluding the ureter. These symptoms indicate need for a thorough cystoscopic examination, including visualization of the renal pelvis and ureter by means of a contrast medium. Intravenous pyelography is helpful as a preliminary procedure. Since bleeding may have its source in any part of the urinary tract, cystoscopic examination always is indicated. In a case in which the patient has lost weight, and has anorexia or a low-grade fever, a thorough urologic study should be included in the diagnostic program.

### *Ureteral Tumors*

Tumors of the ureter are less frequent than those of the kidney. They may be the result of implantation from similar tumors of the kidney, or they may occur primarily in the ureter.

*Case 1*—A 65 year old man consulted his physician because sugar had been found in his urine. He was found to have mild diabetes. He felt well and did not have any discomfort. During the next year he consulted his physician at regular intervals for dietary guidance. On one occasion, urinalysis disclosed a considerable number of red blood cells. Since red blood cells had not been present in his urine at the time of his last examination, the patient was instructed to return in a week for another examination, which also revealed the presence of these cells in the urine. When a third examination also revealed the presence of a considerable number of red cells in the urine, the patient was referred for urologic study.

When ureteral catheterization was attempted, an obstruction was encountered in the lower third of the left ureter. Retrograde pyelography disclosed an irregular constriction of the left ureter (figure 2) and dilatation of the ureter immediately above the constriction. Manipulation of the catheter caused bleeding from the ureteral orifice. A primary infiltrating carcinoma in the lower third of the ureter was found and removed. The patient remains in good health. Fortunately, his physician was aware that blood in the urine could not be influenced by medication.

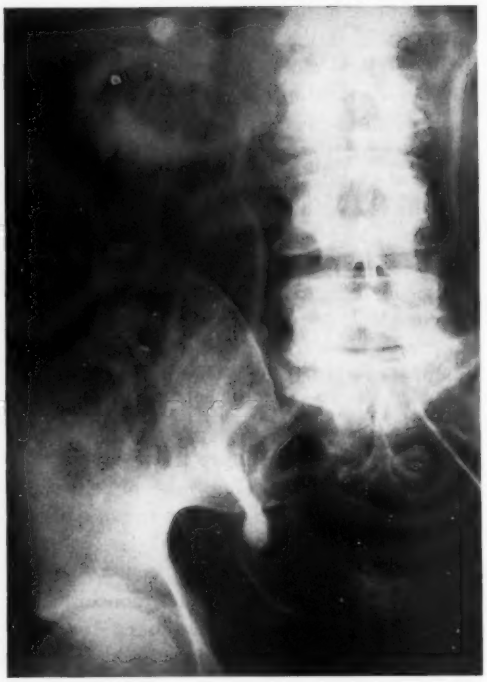

FIGURE 2. Partial obstruction of ureter resulting from primary carcinoma.

### *Tumors of the Urinary Bladder*

Tumors of the bladder vary greatly in the grade of malignancy (figure 3). The symptoms also vary to some extent, depending on the site of the tumor and its physical characteristics. Bleeding is even more frequently encountered in tumors of the bladder than in tumors of the kidney. Bleeding sometimes follows a similar pattern in that it may be spontaneous and rather profuse and may not be noticed macroscopically again for several weeks. While the bleeding from tumors of the bladder cannot definitely be distinguished from that of tumors of the kidney, renal bleeding is likely to have the appearance of old blood, that is, rather dark and sometimes spoken of as a port wine color. Blood from bladder tumors is evacuated more promptly and is likely to be of a brighter color. Clots are also more frequent in bleeding from bladder tumors than in bleeding from tumors of the kidney. Bladder tumors, when situated on the base of the bladder and particularly when near the orifice of the bladder, may cause considerable irritation. This in turn gives rise to urinary frequency, bladder spasms and burning on micturition. Some of the more infiltrating types of tumors do not bleed profusely and blood may be recognized only under the microscope (figure 4).

*Case 2*—A man, aged 75 years, consulted me because he had passed a small amount of pinkish urine three months previously. He thought that some blood had been present in urine which was passed three weeks later. In the meantime, he had not noticed any abnormality. About 30 days after the first attack of hematuria, he became aware that he was voiding more frequently than he had been previously. At the same time, he had had some discomfort which he explained as a sensation that voiding had not been completed following each micturition. This condition gradually had progressed until his rest at night had been so much disturbed that he had decided to consult a doctor.

His urine contained many red blood cells and a moderate number of white blood cells. There was a moderate-sized growth situated just behind the trigone. A small ulcer had oc-

FIGURE 3. Relatively benign papillary tumor of the bladder. Patient living 20 years after removal of tumor.

curred on the base of the bladder and had caused some urgency and frequency of micturition. Infiltration of the bladder wall had occurred, and this rendered the prognosis poor.

The too frequent practice of using some type of medication for blood in the urine results in a false sense of security to the patient, and in many instances permits an operable tumor to extend beyond the limits of surgical removal. I cannot too often reiterate that bleeding is a symptom and should not be treated until its cause has been determined. A careful cystoscopic study following the first evidence of hematuria will result in a higher incidence of cure of malignant tumors of the urinary tract.

### *Tumors of the Urethra*

Papillomas, sometimes spoken of as venereal warts, may occur in the anterior urethra. They most frequently can be seen presenting from the urinary meatus. They may be situated along the entire course of the anterior urethra. They may cause microscopic hematuria or a serosanguineous discharge from the urethral meatus. A diagnosis is made by a careful urethroscopic examination.

Infiltrating carcinoma of the urethra most frequently occurs in or just anterior to the bulbus portion of the urethra.

*Case 3*—A man consulted a urologist because of a slight mucopurulent urethral discharge. This discharge had been present about a month and his urinary stream had become definitely smaller. The urologist dilated his urethra and treated him for a stricture. After the third dilatation at weekly intervals, fever developed and a mass appeared in his perineum. This mass was opened and drained. When drainage had persisted almost 30 days and the mass appeared very little changed in size, the patient consulted a second urologist who obtained a biopsy specimen from the depth of the perineal mass. The diagnosis was adenocarcinoma.

This is not unusual. Tumors of the perineal urethra are more frequently recognized by examining tissue obtained from the depths of what appears to be chronic perineal abscess. A careful history will suggest the presence of a stricture or some obstruction in the urethra. A urethral discharge accompanied by a diminution in the caliber of the urinary stream in a man who has otherwise been normal should create suspicion. A perineal abscess which does not heal promptly after being incised and drained requires exploration and biopsy.

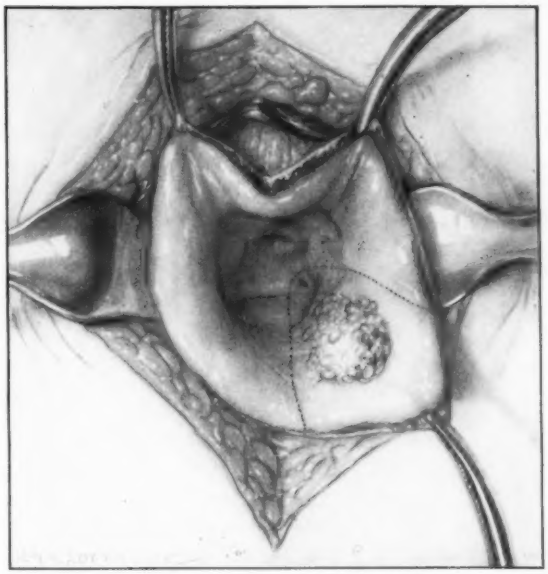

FIGURE 4. Infiltrating carcinoma of the bladder.

### *Tumors of the Penis*

Carcinoma of the penis occurs on or immediately posterior to the glans. The growth may be recognized as a fungating type of lesion or as a clear-cut ulcer with an indurated base (figure 5). The lesion frequently is allowed to advance until a large portion of the glans penis is destroyed before a physician is consulted. In other instances, the lesion is treated with salves or antiseptic dressing in the belief that it is a venereal ulcer. If the patient has a redundant prepuce, the first evidence of malignancy may be a balanitis with a preputial discharge and thickening of the tissues about the preputial orifice which prevents retraction. The tumor may ulcerate through the prepuce.

Men of cancer age do not often contract

FIGURE 5. Carcinoma of the penis.

venereal ulcers. All ulcers should therefore be subjected to thorough diagnostic studies before treatment is instituted. Darkfield illumination will promptly determine whether or not the lesion is syphilitic. A soft, rapidly spreading chancroid will promptly respond to antibiotic medication and cleansing dressings. If the ulcer persists for more than 10 days, a liberal portion should be excised for microscopic examination.

### *Tumors of the Testes*

Tumors of the testes are composed of embryonal tissue. They usually occur in men between the ages of 20 and 35 years. The tumor begins and progresses as a painless enlargement of the testis. If detected early, it may be confined to one area of the testis. In most cases it can be distinguished from inflammatory lesions of the testis by the absence of a history of infection or previous trauma of the urethra and the absence of pus in the urine. Furthermore, if the patient is seen reasonably early, a careful examiner should be able to distinguish the generalized or localized enlargement of the testis from the sausage-shaped enlargement of the epididymis.

The patient may give a history of having had some mild injury of the testis to which he attributes the enlargement. In all cases of tumor of the testis that I have seen, it was apparent that the slight blow on the testis merely called attention to the tumor.

*Case 4*—A physician, about 35 years old, consulted another physician because his left testis appeared different from the right one. There had not been any discomfort or any other incident to call his attention to this condition. It had been discovered while he had been taking a bath. Within 48 hours, a seminoma had been removed and roentgen therapy was being applied to the regional lymph nodes. The patient is living and well 20 years later.

*Case 5*—About 15 years ago, another physician consulted me because while his little child had been playing on the beach he had kicked his father in the testes and had caused moderate pain. While the patient had been dressing, he had examined his testes and had found that one was larger than the other. X-ray treatment for seminoma was begun within 24 hours. The testis was removed two weeks later, resulting in cure.

Any young man with no history of infection who, so far as he knows, has been entirely normal, and who notices a painless, or almost painless, enlargement of the testis deserves immediate investigation. In case of any doubt whatever, the testis should be removed. Biopsy for diagnostic purposes is not wise.

### *Tumors of the Prostate*

Malignant disease of the prostate gland is, in most instances, carcinomatous and occurs during the period of life in which benign hypertrophy of the prostate is to be expected. Occasionally, sarcoma of the prostate is recognized in children or young adults. This tumor grows rapidly, manifests itself as an obstructive lesion of the bladder outlet, and on rectal palpation a large, soft, painless mass is found. It is rapidly fatal.

Carcinoma of the prostate causes the same symptom complex as does benign hypertrophy. When the growth first begins to encroach on the urethra, there is urinary frequency which usually is first manifested by nocturnal fre-

quency. This is followed by progressive difficulty in voiding.

There is little in the history to distinguish one type of prostatic obstruction from another, except that if one questions the patients it will usually be noted that the time from the beginning of urinary frequency to urinary obstruction is much shorter in cases of carcinoma than it is in cases of benign prostatic hypertrophy. It is not unusual for a person with benign hypertrophy of the prostate to give a history of urinary frequency and mild difficulty over a period of four or five years, whereas carcinoma of the prostate will often progress from the earliest symptoms to retention in from one to two years.

*Case 6*—A man consulted his physician because of progressive nocturia. He was 45 years of age, and apparently in normal health except that he was definitely worried about the possibility of malignancy. His father had died of carcinoma of the prostate. Examination showed his prostate to be a little more than normal in size but rather firm and smooth. Catheterization produced about one ounce of residual urine. Endoscopic examination of his urethra and bladder orifice showed what appeared to be a fibrotic constriction at this area. He was advised that a resection of this obstructing tissue would probably give him relief. Following the resection, the tissue submitted to the pathologist showed unmistakable evidence of malignancy. A radical prostatectomy was performed and the patient has an excellent chance for recovery.

Too often the patient does not consult the physician until the carcinoma has extended beyond the confines of the capsule and has become more or less fixed to the surrounding tissues. It is distinguished from the globular, smooth, relatively soft, hypertrophied prostate by irregularity of the surface, the presence of nodules and a dense unyielding nature of the tissue. In case 6, the symptoms evidently resulted from fibrosis of the bladder orifice, and discovery of early prostatic cancer was a fortunate incident.

When the tumor has not extended beyond the gland, cure is possible by a radical prostatectomy. The number of patients so treated will of necessity be small until every physician includes a careful palpation of the prostate in the physical examination of every male patient who presents himself. The presence of an area of irregularity or a nodule that is firmer than the rest of the gland should be an indication for biopsy.

### *Conclusions*

Malignant tumors of the urinary tract and male genital tract are usually heralded by hematuria, pain, a tumor mass, or interference with normal function of the urinary tract. These symptoms do not occur only in cases of malignant disease. When they do occur, a thorough and complete urologic study is indicated.

# Malignant Blood Dyscrasias

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LEUKEMIA and allied diseases of the blood-forming organs cause the deaths of more than 10,000 men, women and children yearly in the United States. Little is known concerning the cause of these catastrophic diseases, and the hereditary and familial characteristics are not well understood. Viruses, chemical compounds and irradiation of various forms have been considered leukemogenic; however, only irradiation has been well established as a leukemogenic agent in man.

The diagnosis of leukemia, malignant lymphoma or multiple myeloma is not difficult in most instances. The diagnosis rests primarily on recognizing findings which suggest the possibility of the underlying disease and applying proper clinical laboratory procedures, such as blood studies, bone marrow aspiration, and biopsy of lymph nodes and the liver or, at times, splenic aspiration. In the final analysis, it is on cytologic and histologic evidence that the diagnosis must be made.

### *Acute Leukemia*

The clinical onset of acute leukemia is often abrupt and simulates that of a febrile disease. Indeed, infection not infrequently accompanies acute leukemia. More often, however, anemia, weakness, fatigability, palpitation and pallor or thrombocytopenic purpura with more dramatic hemorrhagic manifestations usher in the clinical picture. Sore throat or oral lesions accompanied by swollen gums and painful stomatitis are not infrequently the first complaints. In children, bone and joint pain associated with fever, pallor and hemic murmurs may suggest rheumatic fever. In

acute leukemia, the liver, spleen and lymph nodes are usually not enlarged to any extent. Examination of a well-stained blood smear in most instances will reveal a diagnostic blast cell picture. Occasionally, atypical or leukopenic types may require bone marrow aspiration to establish a diagnosis.

### *Chronic Leukemia*

Chronic leukemia usually has an insidious onset. Fatigue and weakness, enlarged lymph nodes, or symptoms arising from splenomegaly are often the first clinical indications of the disease. Nowadays, with the greatly increased performance of routine blood studies, more instances of the disease are discovered incidentally in the preclinical stage of leukemia. Owing to the diffuse, infiltrative character of leukemia, the onset may be bizarre, and coma, priapism or herpes zoster may be the first evidence of the disease. Usually, the diagnosis of leukemia is obvious when the peripheral blood smear is examined. However, leukemoid disorders are more frequent than hitherto suspected and may offer serious problems in diagnosis.

Leukemoid reactions are usually myeloid and may be associated with infections *(especially tuberculosis)*, hemolytic disorders, drug or other hypersensitivity reactions, carcinoma, and the poorly defined group of conditions known as myeloid metaplasia or myeloproliferative disorders. On clinical and hematologic grounds, leukemoid reactions and leukemia may be impossible to differentiate. Recent investigations have shown that, biochemically, neutrophilic leukocytes in chronic myelogenous leukemia are deficient in alkaline phosphatase, while in leukemoid reactions due to infection and other causes the neutrophils have a greatly increased amount of this enzyme.[1,2] Utilization of comparatively simple histochemical technics for alkaline phosphatase determination may afford a practical method for distinguishing most leukemoid states from chronic myelogenous leukemia.[3-5]

### *Malignant Lymphoma*

While malignant blood dyscrasias occur in all age groups, Hodgkin's disease, lymphosarcoma and reticulum cell sarcoma are encountered more commonly in adults than in children. In the great majority of cases, discovery of an enlarged lymph node is the first indication of disease and should logically lead to a biopsy. However, histologic examination of a single lymph node is not an infallible procedure. Inflammatory and other benign changes may simulate a neoplastic disease and lead to an occasional false diagnosis. On the other hand, one lymph node may show a nonspecific picture while removal of a node from another site in the same patient may provide an unequivocal diagnosis of Hodgkin's disease or lymphosarcoma.

In the case of visceral involvement, biopsy may be difficult but should always be attempted if at all practical. Only on this histologic basis can the diagnosis and, hence, the proper therapeutic management and prognosis be based. Occasionally, retroperitoneal Hodgkin's disease with an acute febrile course may justify a trial of nitrogen mustard (HN2); or, x-ray therapy may be employed on an empirical basis.

### *Multiple Myeloma*

This inevitably fatal, nearly always painful, and insidious disease, if not actually greatly increased, is at least now seen with much greater frequency than ever before in clinical practice. In general, it is a disease of older age groups with a peak of incidence at age 60. It is more common in men than in women, and seldom affects persons who are less than 30 years of age. The usual onset is that of most malignant diseases, with weakness and weight loss but, most importantly, with pain—usually backache. The combination of pallor and pain in the back in an old person should at once raise the possibility of multiple myeloma. Infections, no doubt due to poor immune mechanism in elderly persons, may first call attention to the underlying disease. Pathologic fractures, neurologic involvement from contiguous plasma cell tumors, or compression of collapsed vertebrae are other early clinical manifestations of the disease.

In some cases, only a profound, unexplained anemia may be present, and on bone marrow

aspiration the diagnosis will be apparent. Other highly suggestive laboratory findings may be present, such as "greasiness" of the blood smears, pseudoagglutination and marked rouleau formation, a very rapid sedimentation rate of the erythrocytes, hyperglobulinemia, proteinuria and osteolytic lesions noted by x-ray examination. Multiple myeloma may be confused with other diseases in which greatly increased numbers of plasma cells appear in the bone marrow, and there is an associated hyperglobulinemia. However, except in rare instances, the bone marrow picture of "sheets" of myeloma cells with associated bone lesions, biochemical changes in the plasma and, often, proteinuria with Bence Jones protein will indicate the correct diagnosis.

### *Conclusion*

One might say that in dealing with diagnostic problems, whether concerned with malignant blood dyscrasias or with other obscure disease processes, one could paraphrase Pasteur's dictum and state that "Diagnoses come only to the mind that is prepared to receive them."

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*40th Annual Interstate Postgraduate Medical Association Assembly*
*Milwaukee, Wisconsin, November 14-17, 1955*

## A PANEL DISCUSSION ON MULTIPLE SCLEROSIS

Presentation of clinical cases demonstrating the various aspects and stages of multiple sclerosis. Case histories with associated clinical findings and laboratory studies used in the differential diagnoses of the cases will be presented. Therapy utilized in the different cases with its results will be outlined. Some of the common neurologic objective findings will be demonstrated. The various typical and atypical modes of onset and course of this disease process will be demonstrated by the cases presented. Discussion among the various members of the panel on the validity of the diagnoses and treatment of the cases will be presented.

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# Diagnosis of Uterine and Ovarian Cancer

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### *Carcinoma of the Cervix and Fundus of the Uterus*

THE diagnosis of advanced carcinoma of the cervix, that is, an ulcerative or exophytic lesion which occupies a major portion of the cervix and has extended to the vagina and broad ligaments, is not difficult. The gross appearance of such a lesion is characteristic. The confirmation of the presumptive diagnosis is hardly more difficult since it is easy to obtain biopsic material, and microscopic examination nearly always will disclose the true nature of the lesion.

This much has been known since biopsy was devised by Virchow more than 100 years ago. Physicians still can learn much about advanced carcinoma of the cervix, and they need to know more if the results of treatment are to be improved.

In recent years, it has seemed much more desirable to detect malignant lesions in the early stage of their development and to utilize methods that will insure the institution of treatment before extensive outgrowth or metastasis has occurred. Instead of emphasizing the pathologic significance of a serous or sanguineous discharge, physicians are urging that all women who are between 35 and 60 years of age, especially women who have borne children, should consult their family physician at least once a year, regardless of whether or not they have had any symptoms referable to the vagina, breast or gastrointestinal tract.

The rationale of this approach is simple. If cancer can be detected in its early stage of development, and if treatment can be instituted promptly, it *very* often can be cured. Advanced cancer frequently is incurable. If it can be cured or if adequate palliation can be obtained, the side effects are severe and should be avoided if possible. When a woman consults her physician for a check-up, he should pay particular attention to those organs that are most likely to be the site of a cancer.

Cancer of the cervix and cancer of the

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fundus are very different lesions. A bleeding or discharging cancer of the cervix usually is an advanced lesion, whereas early cancer is quite silent. It must be sought if it is to be found at an early stage. On the other hand, cancer of the endometrium seeps serous fluid and bleeds at an early stage of development. Bleeding, therefore, is an important symptom. Furthermore, the body of the uterus is a good barrier against endometrial cancer, and there seems to be a tendency toward slower invasiveness here than in cancer of the cervix. As a result, there is a longer stage of latency, which increases the chance for successful recognition and treatment.

The methods used to clinch the clinical suspicion of cancer of the uterus usually are well known. Cervical biopsy is a very useful aid, especially when the significant area is successfully chosen for tissue removal. To aid in selecting those areas most likely to be the site of an early malignant lesion, the use of the iodine, or Schiller's, test is advocated by many. However, I have not found it especially helpful. As has been pointed out, the result of a single biopsy may not be informative or sufficiently conclusive. Therefore, the so-called four-point biopsy has been advocated. This, of course, could conceivably result in removing a considerable portion of the portio vaginalis if carried out on the same patient over a period of years. However, this is the acme of the biopsy effort and is a very important diagnostic aid.

In places in which there are pathologists who have been trained in the diagnosis of cancer by special cytologic methods, physicians have a diagnostic procedure that is particularly applicable to the detection of early cancer of the uterus. In cases in which this procedure is used, an aliquot sample of cells is obtained without the removal of tissue. This method of diagnosis will detect the presence of cancer in the preulcerative or preinvasive stage. In places in which the services of such trained pathologists are available, I would strongly urge their use as an adjuvant to cervical or endometrial biopsy.

Since the cytologic diagnosis of carcinoma of the fundus is more difficult than the cytologic diagnosis of cancer of the cervix, it is thought to be less reliable. Cancer of the fundus, however, can be detected with a high degree of accuracy by pathologists who have been trained in cytologic diagnosis. In places in which such a trained pathologist is not available, I advise diagnostic uterine curettage in cases in which the presence of endometrial cancer seems possible. Since endometrial cancer is always localized in its early stages, I feel that thorough curettage should be performed in the hospital and that anesthesia should be used. The unreliable office curettement with a suction apparatus is hardly adequate except in cases of advanced cancer in which the lesions are extensive. Recognition of early cancer by office curettage is purely a matter of chance. I, therefore, advocate the cytologic examination of smears. In cases in which the diagnosis is still in doubt, I advise diagnostic curettage in the hospital.

### *Carcinoma of the Ovary*

Cancer of the ovary is a relatively rare and, unhappily, a very silent lesion. As a rule, it does not cause any symptoms until it is very advanced, that is, until it is large enough to produce mechanical symptoms either due to the development of large masses in the abdomen or by the secretion of ascitic fluid, which distends the abdomen. These are the symptoms which bring the patient to the physician, and they are due to advanced lesions. How fortunate is the patient who, because of frequent check-ups by her doctor, is apprised of the presence of a small early lesion. This is the desirable situation, as much can be done to help the patient under these circumstances.

The diagnosis is usually made by bimanual vaginoabdominal examination. Ovarian cancers are very often cystic, and usually are 8 to 10 cm. in diameter. Small cysts, 2 to 4 cm. in diameter, are usually graafian follicle, corpus luteum or endometrial cysts. Very large cysts are ordinarily serous or pseudomucinous cystadenomas, and may or may not be malignant. Nodules palpable in the cul-de-sac of Douglas are strongly suggestive of peritoneal implants of papillary processes, especially if accompanied by ascites. When ascites is pres-

ent it is useful to tap the abdomen and drain off ascitic fluid. This should be centrifuged, and the sediment should be fixed and stained for microscopic study. Not infrequently, especially in the serous types of cystadenomas, the typical cells and rosettes may be demonstrated, and thus the diagnosis of carcinoma made or strongly suggested. More often, the diagnosis cannot be made until the abdomen is opened and tissue secured for microscopic study.

The finding of pelvic cysts or neoplasms always poses the problem as to whether the abdomen must be opened and operative procedures applied or whether the best interests of the patient may be served by continuous observation. If, as often happens in the case of small cysts, natural processes take care of the growth, a major surgical procedure has been avoided safely. However, when cysts are large, and especially when they are bosselated and contain solid tissue, or when the tumor is solid rather than cystic, it usually is advisable to open the abdomen. If there are shotty nodules in the cul-de-sac of Douglas and/or ascites, the abdomen usually should be opened if the diagnosis is to be confirmed adequately.

### *The Annual Gynecologic Check-up*

If cancer of the uterus or ovary is to be detected in the early stage, and if the patient is to be given the best chance for a cure, all women between 35 and 60 years of age should have a gynecologic examination at least once a year. In the course of this examination, the physician should look carefully for cancer of the uterus or ovary. This will require a new point of view on the part of both physicians and patients.

## *Postgraduate Clinical* NOTES

### 37. GAINS AGAINST CANCER

The following major gains against cancer are cited in the 1952-54 biennial report of Memorial Center for Cancer and Allied Diseases with its research unit, the Sloan-Kettering Institute, New York.

1) The mass and sustained growth, for the first time, of human cancers in laboratory animals.

2) Improvement from 6 per cent to 39.5 per cent in cure rates for soft tissue sarcomas over the past 20 years.

3) Synthesis by the Wellcome Research Laboratories of 6-mercaptopurine, a chemical that appears from tests at Memorial to be one of the most effective in restraining acute leukemia.

4) An increase through the years from 10 to 75 per cent in the number of patients with cancer of the stomach who can be treated surgically.

5) Establishment of circumcision of male infants as a practical means for partial prevention of cervical cancer in women.

6) Improvement in techniques of surgery of the liver permitting removal of cancer in this vital organ in some selected cases.

7) Development of effective treatment for formerly uncontrollable small blood vessel tumors (hemorrhagic telangiectasia).

8) Adaptation of a virus to destroy, rapidly and completely, human cancer cells of one type in the test tube.

9) Definition of two types of breast cancer, each requiring different treatment.

10) Discovery that cortisone, as well as sex hormones, will temporarily control some advanced breast cancers.

*Science*, January 21, 1955, p. 84

# Gastric Carcinoma and Sarcoma

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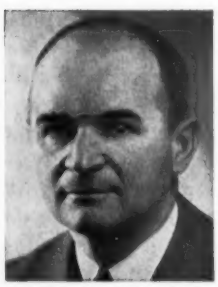

WALTMAN WALTERS

In a symposium on "Advances in Treatment of Cancer of the Stomach," presented before the staff of the Mayo Clinic in 1952, one of the participants, Comfort,[1] in discussing the problem of gastric cancer from the viewpoint of the internist, commented as follows: "The problem of gastric cancer, like many other problems facing the medical profession today, is a challenging one. How well are we solving it? How may we improve our results? What methods are being considered?"

About 1940, Walters, Gray and Priestley[2-4] with the collaboration of Berkson and Lewis recorded the results of surgical treatment of cancer of the stomach at the Mayo Clinic from the years 1907 to 1938 inclusive. It was our purpose in 1952 to give a brief companion report[5] on the patients operated on from 1939 to 1950 inclusive, and to contrast the results of treatment in the two periods, even though the number of patients and the span of years were unequal numerically. We hoped from this study to determine the effects of surgical progress and to arrive at some conclusion as to how results could be improved further. In the second period remarkable increases were noted in the exploratory, the resectability and the survival rates, and a marked reduction occurred in the mortality rate. The survival rate had increased in the second period more than 180 per cent[6] over that in the first period. Stated in another way: Of all the patients with cancer of the stomach, whether operable or inoperable, who entered the Mayo Clinic in the early period, 5 per cent were living five years later. Of those entering in the second period 14 per cent were living five years later. When one eliminates the patients who were

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not operated on and considers only those who had operable lesions, these interesting data are noted: The exploratory rate had increased more than 33 per cent, the resectability rate 48 per cent, and the mortality rate had decreased (from 15.2 to 6.2 per cent, an improvement in outlook of about 100 per cent).

In the statistical data presented, the increases in operability and resectability rates were due to the performance of more extensive gastric resections and more total gastrectomies—and with increasing experience plus the aids obtained by adequate preoperative preparation and postoperative care, the mortality rates had lessened appreciably. For example, up through 1939 total gastrectomy was performed only 34 times with a mortality rate of 66 per cent,[5] while from 1940 through 1950 it was performed 187 times[7] with an average mortality rate of about 13 per cent.

Each year subsequent to 1950 approximately 25 to 30 patients have had total gastrectomy at the Clinic, and from 106 to 140 have had partial gastrectomy for malignant lesions of the stomach.[8-10] The mortality rate for partial gastrectomy for malignant lesions averaged 7.9, 1.9 and 5.1 per cent in 1951, 1952 and 1953, respectively. In these three years, a total of 364 patients underwent partial gastrectomy for malignant lesions of the stomach. The decrease in mortality rate was due to many factors. Preoperative and postoperative blood transfusions and intravenous administration of fluids and electrolytes as needed played important roles, and scientific methods of proper selection and administration of anesthetics with aspiration of mucus from the bronchial passages were important contributions. So was the use of the antibiotics according to bacterial studies and comparative sensitization tests. Increasing experience in the technics of both partial and total gastrectomies also played an important role.

In measuring the influence of these improved results on the outlook for patients having cancer of the stomach, it was noted that the five year survival rate in the early group after resection was 28.6 per cent,[4] whereas in the entire group it was 31.6 per cent. When all the lesions removed by resection from 1907 through 1949 were studied from the standpoint of Broders' grading of malignancy, it was found that 56.8 per cent of the patients with malignant lesions of grades 1 and 2; 31.4 per cent, grade 3; and 22.8 per cent, grade 4, were living at the end of five years,[5] whereas 89.0 per cent of the normal population survived for this period. However, 20 per cent of the patients had hopeless inoperable lesions on admission. Although 80 per cent had undergone surgical exploration, 36 per cent did not have resectable lesions. Of the 44 per cent who had resectable lesions, 68 per cent died within five years of the operation.

These figures seem to indicate that the greatest field for improvement now is in that group judged inoperable on physical examination, and those lesions found not resectable at laparotomy, for together they form 56 per cent of the total. We must concentrate the effort toward earlier diagnosis and earlier treatment to decrease the percentages in these groups.

How can an earlier diagnosis be made? In my experience, covering more than 31 years in the surgical treatment of lesions of the upper part of the abdomen, the patients I have seen with gastric lesions too extensive to be removed have usually had long histories of dyspepsia, and operation has been delayed unnecessarily. As for those lesions which prove inoperable, they are the ones with extension to irremovable structures or with metastasis in the liver or throughout the abdomen. These are usually the highly malignant lesions. Then there are the infiltrating lesions, the scirrhous or "leather bottle" type of carcinoma. Ever so many of them gave symptoms at an early period indicating diseases of stomach or duodenum, but unfortunately the symptoms were misinterpreted by either patient or physician (including roentgenologist and gastroscopist in some cases). The most misleading group of symptoms were those simulating other upper abdominal lesions. Several will be considered.

### *Carcinoma Simulating Duodenal Ulcer*

In our early studies recorded in 1940, we were astonished at the number of patients

with cancer of the stomach who gave an early history which simulated that of benign peptic ulcer. In fact, one-third of all the patients operated on for cancer of the stomach had such an ulcer history in the early period of their disease. Equally startling was the fact that 80 per cent of these patients responded to a medical regimen for ulcer. These two facts, I think, should occupy a most important place in the thoughts of a physician seeing a patient who gives an ulcer history. He should be particularly concerned with the fact that the favorable response to a medical regimen, meaning usually relief of pain or distressing discomfort, can be misleading as a diagnostic test of benignancy.

In my student days, the late Bertram W. Sippy emphasized to the members of the class that a patient who had an ulcerlike type of history was sure to have an ulcer, and that it was most certain to be an ulcer if the patient responded to a medical regimen consisting of neutralization of gastric acids with alkalis and milk and a bland diet to reduce gastric hypermotility. However, such is not the case! Nor is the history of ulcer or the response to a medical regimen alone at fault. Unfortunately in an occasional rare case the roentgenologist may miss a lesion on the posterior wall of the stomach, especially one high on the posterior wall, or may assume that what seems to be an obstructing lesion in the duodenum or in the vicinity of the pylorus is duodenal and benign when actually it is in the stomach and malignant.

The duration of ulcerlike symptoms over a long period may be further misleading.

For example: A woman had had ulcerlike distress for 22 years and a roentgenographic diagnosis had been made of duodenal ulcer. At operation a colloid adenocarcinoma, grade 1, was situated at the pyloric end of the stomach and no duodenal ulcer could be identified. Partial gastrectomy, of the Billroth I type, was performed.

In some patients with a history of peptic ulcer on whom the roentgenographic examination has not been too satisfactory and gastroscopic examination is performed, the gastroscopist may be able to locate the lesion, and in many instances determine whether it is benign or malignant. However, there are some spots in the stomach hidden to view through the gastroscope. Lesions situated on the posterior wall in the fundus and near the pylorus cannot be seen through the gastroscope. Moreover, certain gastric lesions in other locations will escape gastroscopic detection and this should be kept in mind.

How could the diagnosis of carcinoma have been made earlier in these cases? It seems to me that whenever patients have persistent dyspepsia which has not responded to medical therapy, and whenever the exact diagnosis or the location of the lesion is uncertain, abdominal exploration is indicated. One would expect that gastric tumors could be palpated through the abdominal wall and many large ones are, but many small and infiltrating ones cannot be. In fact, I have frequently not been able to palpate the extensive gastric lesions of linitis plastica.

I would favor exploration of all ulcerating lesions of the stomach which have been present for more than a few months in patients of middle age, or older, especially if gastric acidity is low and providing the patient has had a trial of a scientifically carried out medical program in the hopes of healing the ulcer. If the ulcer has seemed to heal by virtue of relief of symptoms, as evidenced by disappearance of the niche on the roentgenographic examination of the stomach, the patient should still be a cancer suspect and be examined physically and roentgenographically at intervals of three months. If uncertainty exists, gastroscopic examination should be carried out also to exclude the possibility that the lesion might have been malignant and the niche had not really healed but had just granulated over temporarily. One of the most helpful tests, now unfortunately sometimes omitted, is a test of gastric acidity after an Ewald test meal. If achlorhydria is present, the lesion is practically always malignant, for although 50 per cent of the patients with gastric carcinomas have some free hydrochloric acid in their gastric secretion, in all but 10 per cent it is much lower than that usually found in association with benign peptic ulcerations.

I think that the astute clinician has prevented mistakes in some cases of early gastric carcinoma by being unwilling, in view of the patient's history of persistent dyspepsia or persistent discomfort, especially after eating, to accept an x-ray report of "normal stomach and duodenum," even when the evidence of negativity seemed reinforced by a negative gastroscopic examination. Such a clinician frequently has had the examinations repeated after discussing the problem with both the roentgenologist and gastroscopist, and at the second or third try the lesion has been found. Moreover, the frequent association of an ulcerlike history with gastric carcinoma means that no patient with such a history should be treated by nonsurgical methods without a thorough roentgenographic examination of the gastroduodenal region, and, in cases of doubt, without a gastroscopic examination. Unfortunately, cytologic studies of gastric contents for malignant gastric mucosal cells have not been too helpful in identifying malignant gastric lesions, especially of carcinomas infiltrating the gastric wall. This type of lesion is difficult too for the roentgenologist to identify. The papillary lesions from which exfoliating cells might be obtained by a stomach tube with and without a cureting edge are readily demonstrated roentgenographically even when only the size of a finger nail.

### *Symptoms of Gastrointestinal Dysfunction*

One cannot help but be impressed in all cases of cancer of the stomach, with the possible exception of the insidious, slowly developing carcinoma of linitis plastica, that the patient's general health has been impaired for a long period. Frequently, the only symptom has been one of discomfort, a vague dyspepsia, but this has been a *persisting* discomfort, and a *persisting* dyspepsia lasting for most of the time for weeks or months and coming with some definite relationship to meals. Weakness due to insufficient intake of food is soon followed by loss of weight and anemia, and these are all important indicators of the possibility of a serious gastrointestinal or other intra-abdominal lesion. I believe that in such cases the routine examination should always consist of a study of gastric acids, roentgenographic examination of stomach, duodenum and, wherever it is indicated, of the colon, plus a proctoscopic examination and a study of the sedimentation rate, for an elevated rate indicates sickness.

### *Scirrhous Carcinoma*

Scirrhous carcinoma of the stomach, which is aptly called "leather bottle stomach," is the carcinoma which is most likely to be overlooked, in my experience. This is largely due to the fact that these lesions infiltrate the wall of the stomach, seldom bleed or ulcerate and are not obstructive until late. Because it does not project into the interior of the stomach, it is frequently overlooked by the roentgenologist. Most of the patients, however, have achlorhydria. Therefore, persistent dyspepsia or persistent discomfort in any patient who has achlorhydria should lead one to suspect immediately that the patient has an infiltrating malignant lesion of the stomach.

Most of the scirrhous carcinomas for which I have operated have involved the stomach extensively, and most of these patients have had a long history of gastric dyspepsia. In many of them previous roentgenograms have been taken and the nature of the lesion has not been recognized by experienced roentgenologists. In a few of these cases a review of the roentgenograms suggests that the lesion should have been recognized. Some such patients, unfortunately, have been told that the lesion was a gastric ulcer and treated medically. Here again it is sometimes difficult to understand how such an erroneous diagnosis could be made on the evidence in the roentgenogram that the patient presents.

The following case is one in point.

The patient was examined in August 1954, when she was 54 years of age. She dated her stomach trouble from October 1953, and described it as distress usually with meals. The physician in her home locality ascribed it to nervousness, but roentgenograms at that time revealed a small gastric ulcer, according to the patient. The patient's pain sometimes extended to the right shoulder. In January and

February 1954, she became worse. A roentgenogram at that time showed a suggestion of a duodenal ulcer.

On examination at the Mayo Clinic in August 1954, the patient was found to have achlorhydria, and x-ray examination showed a scirrhous carcinoma diffusely involving the entire stomach from the cardia to the pylorus. In August 1954, I performed total gastrectomy with removal of the stomach, the gastrocolic and gastrohepatic omentum. The lesion was a scirrhous carcinoma, grade 4, involving the entire stomach and the lymph nodes along both greater and lesser curvatures. The patient is living and well at the present time (February 16, 1955).

It seems to me the error in this case could have been avoided by repeated fluoroscopic and roentgenographic examinations and the proper interpretation of both. The roentgenogram of her stomach (figure 1) taken just before her operation shows an extensive infiltrating gastric lesion of the linitis plastica type as did the roentgenogram taken eight months previously which the patient brought with her.

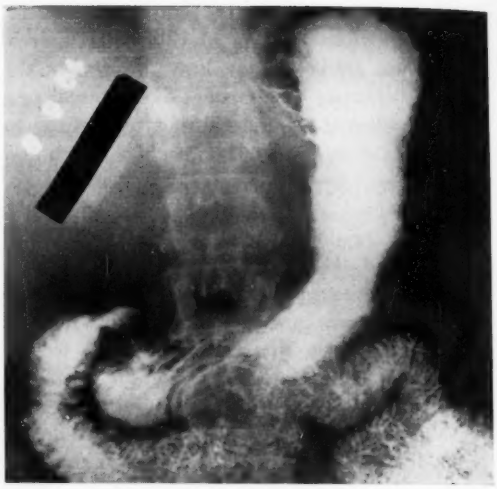

FIGURE 1. Scirrhous carcinoma of the stomach diagnosed elsewhere first as a gastric and then as a duodenal ulcer eight months previously.

### *Sarcoma*

Each year a definite number of patients operated on are found to have sarcomas of the stomach, usually lymphosarcomas with an occasional leiomyosarcoma. In 1953,[10] there were 211 patients with adenocarcinoma and 12 with lymphosarcoma of the stomach operated on (5.6 per cent) at the Mayo Clinic. In 1952, 6.9 per cent[9] of the stomachs resected for malignant lesions contained sarcomas, and in 1951, 3.7 per cent.[8]

These lesions are usually indistinguishable from the adenocarcinomas by x-ray examination and sometimes difficult to distinguish at operation. However, lymphosarcomas usually are more infiltrating than carcinomas and are associated with larger and often whiter lymph nodes in the gastric omenta. They occur more frequently in patients in the younger age groups (those less than 45 years of age) than do the adenocarcinomas. Their response to x-ray therapy is frequently remarkable; however, I believe that when the lesion is resectable this should be done and x-ray therapy given postoperatively—not too early, however, for fear of interfering with solid healing of the suture line in case the lesion has extended beyond the limit of resection. In any case in which for any reason a gastric lesion appears irremovable, the surgeon must ascertain that the lesion is carcinomatous and is not sarcomatous or a diffuse inflammatory or granulomatous lesion. A small piece of the lesion and also one of the enlarged adjacent lymph nodes should be removed for microscopic examination, because if the lesion is a lymphosarcoma, x-ray therapy may cause it to recede with relief of symptoms.

### *Diffuse Inflammatory Gastric Lesions Simulating Carcinoma*

In our 1940 study, my colleagues and I[2] were surprised to find that 0.4 per cent of patients who were found at operation to have inoperable gastric lesions lived beyond a five year period. In a critical review we noted that biopsies of the lesions had not been made in about half of these cases. Practically all lesions involved much of the stomach and had extended or perforated to adjacent viscera with fixation. In these cases it is conceivable that

the surgeon thought excision of a specimen of the tumor for biopsy might open into the lumen of the stomach, and because of the tumorous involvement of the gastric wall, healing might not follow closure, and leakage with peritonitis might occur. Practically all of the lesions which were not biopsied were undoubtedly benign, and similar to the ligneous infection or woody infection in the wall of the cecum secondary to an adherent appendix which becomes repeatedly inflamed. The cause of ligneous infection of the stomach is usually a large diffuse gastric ulcer which has perforated posteriorly into the pancreas or the transverse mesocolon or both and has extended around and involved the anterior wall of the stomach.*

In a few of the patients with inoperable lesions who survived five years, biopsy of the lesion or the lymph nodes revealed a malignant lesion. The five year survival was probably due to the low degree of malignancy of the lesion and the individual's tissue resistance to an extension of the lesion.

The corollary of all this is that one should never give a hopeless prognosis to a patient with a seemingly inoperable lesion of the stomach unless microscopic examination proves the lesion to be carcinomatous. Moreover, some gastric lesions which are sarcomatous on frozen-section microscopic examination are undistinguishable from the small round-cell highly malignant adenocarcinomas and the later diagnosis may be made prematurely before formalin-fixed sections which permit differentiation of the lesions are studied. In these cases, or others, in which the differential diagnosis between the two lesions is in doubt, I usually advise postoperative x-ray therapy. In cases of this type in which a hopeless prognosis has been conveyed to the patient but x-ray therapy has been given, the patient has sometimes consulted an irregular practitioner as a last resort. The treatment then given, which may consist of serums, vaccines, manipulations or suprasonic rays, may receive the credit for the "cure" which x-ray therapy actually has effected.

*Healing of the ulcer probably occurs from a medical regimen similar to that usually employed for peptic ulcer.


***Summary***

Remarkable improvements in the treatment of malignant lesions of the stomach have increased the five year survival rate by more than 180 per cent[6] in about 10 years. This increase has been due not alone to the increase in the percentage of patients whose lesions have been removed by more extensive resection but to a better understanding of how to prepare patients for operation by use of antibiotics when necessary, by better anesthesia, and by a better program of postoperative care based on the physiologic requirements of each patient; together these have greatly reduced the mortality rates following the operation.

Unfortunately 20 of each 100 patients with malignant gastric lesions coming to the Mayo Clinic from 1940 to 1950 were judged to have inoperable lesions[5] on physical examination, and an additional 36 had lesions which were found at laparotomy to be inoperable. This means that 56 of each 100 patients lost their chance for the average 31.6 per cent five year survival rate, which obtains when the lesion is recognized early enough to permit its surgical removal.

A review of thousands of cases of cancer of the stomach encountered at the Mayo Clinic disclosed that common causes of delay in recognizing the lesions were: (1) an erroneous diagnosis of benign peptic ulcer (33 per cent of our patients operated on have had a history of ulcer), with treatment for ulcer without x-ray examinations of the stomach and duodenum on the assumption that the lesion was duodenal and hence benign, (2) relief of symptoms by a medical regimen for ulcer leading to the erroneous clinical interpretation that the ulcer was benign, and (3) prolonged medical treatment of roentgenologically diagnosed "ulcers of the stomach" without repeated roentgenographic and gastroscopic examinations when indicated to see whether the ulcer had healed. Eighty per cent of patients operated on at the Mayo Clinic for gastric carcinoma who had histories typical of ulcer were relieved of symptoms, sometimes for months and sometimes for years, by a medical ulcer regimen. Repeated x-ray exami-

nations of such patients are necessary, since the craters of some small ulcerating gastric carcinomas fill in temporarily with granulation tissue giving an erroneous x-ray picture of healing.

Other common causes of delay are (4) failure to recognize the significance of achlorhydria on gastric analysis and the value of gastric analyses in all middle-aged patients with dyspepsia, (5) failure to recognize the value of abdominal exploration in patients with persistent dyspepsia or epigastric discomfort, especially when there has been loss of weight with and without anemia, (6) failure to recognize that large gastric tumors may not be palpable because of their high location in the stomach (under the costal margin), and (7) failure to persist in a clinical diagnosis and insist on abdominal exploration (at practically no risk and with but a few days' hospitalization), when x-ray examinations of stomach and duodenum have failed to demonstrate a lesion. In these cases gastroscopic examination by an experienced gastroscopist has been helpful, if not in identifying the lesion, then by noting the presence of abnormal changes within the lumen of the stomach. Another common cause of delay in identifying the true character of the lesion is due to failure to advise removal of gastric polyps that may be malignant. Most of the polyps bleed slightly and are associated with anemia.

Sarcoma of the stomach usually cannot be distinguished from carcinoma prior to operation. The sarcomas of the stomach are usually lymphosarcomas. They occur in the stomach in the proportion of about 5 to 100 carcinomas. I believe in resection with surgical removal of the lesion if possible, and if the lesion is a lymphosarcoma, x-ray therapy some weeks after surgical removal should be given when healing of the anastomosis is complete.

One must make certain that inoperable gastric lesions are malignant and carcinomatous by biopsy with microscopic examination of both frozen and formalin-fixed sections of tissue. This is especially important to exclude a sarcomatous lesion sensitive to destruction by x-ray therapy.

Gastric polyps, like polyps of the colon, should be removed. Many are malignant at the time of removal and possibly many become malignant from the mechanical friction by food and by irritation from heat in food and drink.

In the final analysis, earlier recognition of the presence of a gastric malignancy is in the hands of the family physician and the internist when they first see and treat patients with a persistent dyspeptic discomfort. It is possible for them with modern methods of diagnosis and with the knowledge that malignant gastric lesions may masquerade as benign ones to determine the need or the advantages of earlier operation and of abdominal exploration.

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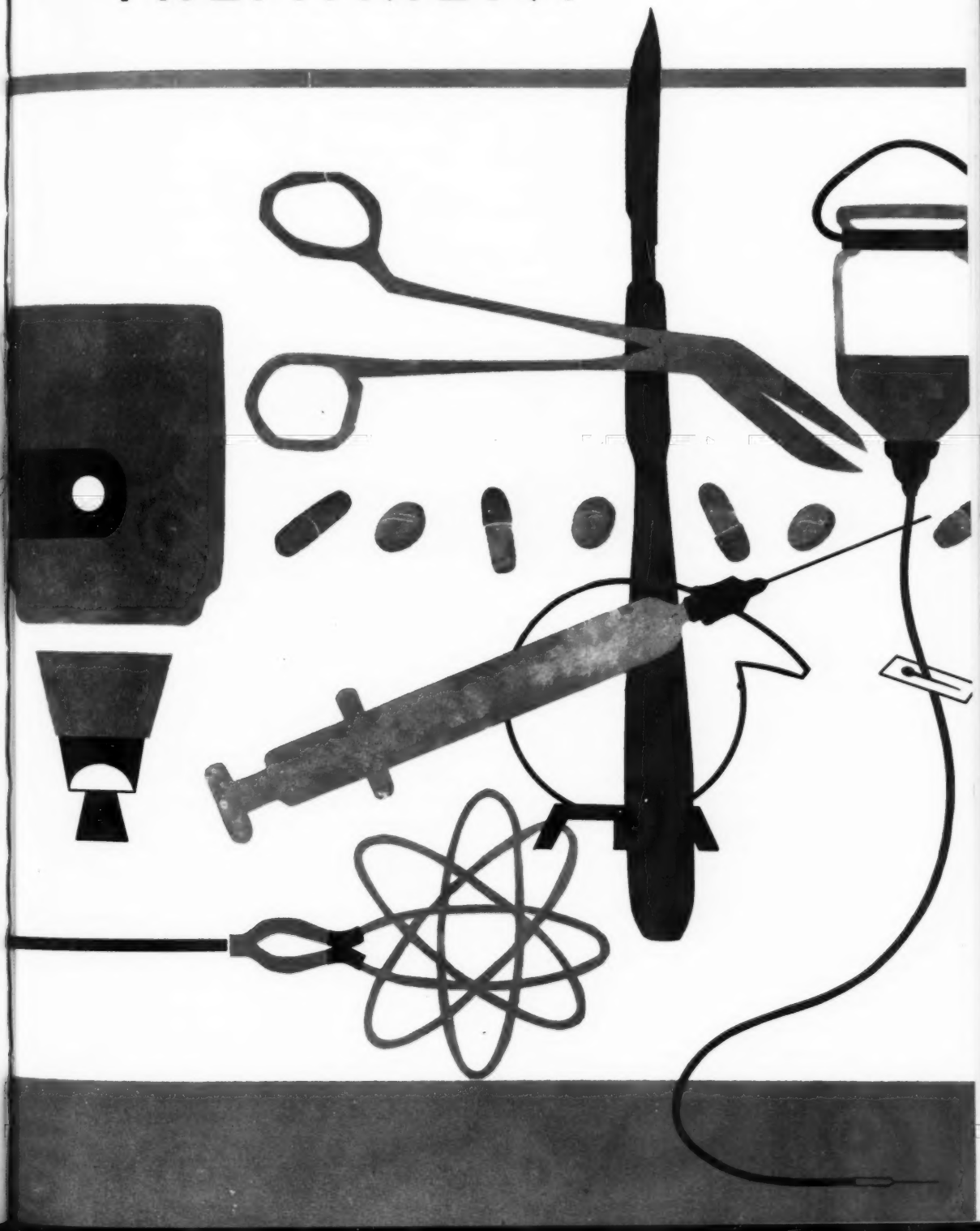
# TREATMENT



# Special Therapeutic Problems in Gynecologic Cancer

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THERAPEUTIC problems in gynecologic cancer are as varied and complex as in any of the disciplines or anatomic ranges of study for malignant disease. The problems begin with diagnosis. Error at that stage can result in therapeutic failure. Missed diagnosis may cause untoward delay in definitive measures, or, in the presence of a lesion believed to be benign, the corrective procedure may complicate the situation beyond repair. The importance of such diagnostic procedures as the Schiller reaction, vaginal smear examination, biopsy (including endometrial), and curettement cannot be overestimated. It is far better to perform those procedures, sometimes unnecessarily, than to risk their omission in a single case of cancer. They are indicated in the presence of tumefaction, induration, any abnormal showing of blood, and discharge in any form. The presence of a thin watery discharge, sometimes mistaken for urine, is always significant. It should be noted, of course, that definitive diagnosis is made only by biopsy. Under no circumstances should treatment be applied for cancer on the basis of iodine response or vaginal smear alone.

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### *Intra-epithelial Cervical Cancer*

One of the common dilemmas in diagnosis is the presence of intra-epithelial cancer. Two pertinent questions arise: (1) Does the *in situ* process extend beyond limits of the cervix? (2) Is the lesion truly noninvasive? The first question can be answered rather effectively by painting the vagina with Lugol's solution. Biopsic specimens should be examined from areas failing to stain. Extension into the vaginal epithelium is not uncommon, and at times the length of that structure may be involved. Then the question of an invasion is more difficult to evaluate. Search for invasion should include curettement of the cervical canal, keeping that tissue separate from scrapings taken deeper in the uterine cavity, and cervical biopsy representative of the entire region about the external os.

The natural history of intra-epithelial cancer is obscure. Spontaneous regression may be possible. It is believed more probable in association with pregnancy, but some authors attribute that experience to the misinterpretation of normal histologic changes associated with gestation. On the other hand, certain cases of intra-epithelial cancer, believed to be well documented, have been followed to true invasion. It has been stated that we may never

know the true answer because the cervix must be removed and sectioned serially to prove absence of invasion, and that the cervix must be left undisturbed to prove capability for progression to invasive cancer. The pertinent point to be made here is that clinically evident cancer is so frequently associated with areas of the *in situ* type that every suspected example should be thoroughly investigated for invasion. Importance for that distinction is found in differences in methods of treatment.

An established diagnosis of intra-epithelial cancer does not create an emergency requiring immediate radical treatment. The average age of onset is approximately a decade younger than that for clinically evident cervical cancer. An estimate of the time required for transition to invasion is from 1 to 10 years. A young woman desiring children may be observed for an appropriate period. In association with pregnancy, the fetus may be allowed to go to term for delivery by a method deemed appropriate at that time. There is, however, uniform agreement that treatment is indicated for those in whom family is complete, or for patients past the childbearing age. In younger women, a minimal procedure of hysterectomy allows preservation of ovarian function, but in postmenopausal patients it is believed that treatment by surgery or irradiation should be of the radical quality employed in clinically evident cancer. Mention should again be made of vaginal involvement. In such instances an appropriate segment of the vaginal tube must be included in the therapeutic procedure to be applied.

### *Pregnancy and Cervical Cancer*

Another important therapeutic problem is related to instances of cancer complicated by pregnancy. While such cases are relatively uncommon they usually involve lesions of the cervix. It is not the intent to discuss here the effects of pregnancy on the tumor, nor the possibility of injury to fetal tissues by irradiation. The immediate problems include disposition of the pregnancy and management of the cervical lesion. Favorable statistical results in such cases fall below the average for nongravid patients.

Prognosis during the first trimester of pregnancy is, however, about equal to that for other cases of cervical cancer in the same stages of tumor advance. In those patients, preservation of the fetus is impractical and cannot be accomplished in the face of consequences from tumor growth. Furthermore, discharge of fetal parts through the birth canal does not necessitate excessive cervical dilatation. Treatment by irradiation can usually be performed without serious interruption. Fetal death occurs during the administration of x-rays, and abortion often takes place during or immediately after that time. The application of radium rarely need be delayed for longer than two weeks following roentgen treatment. Radical hysterectomy can be performed without too much inconvenience from uterine size or edema of tissues, if surgery is selected as the method of treatment.

Different conditions prevail during the second trimester. Size of the uterus and changes in normal tissue hinder the surgical procedure. When the fetus has been killed by irradiation, it may cause untoward dilatation if it is then allowed to pass through the cervix. Hysterotomy offers a means of ending the pregnancy, and irradiation may be extended for a period long enough to allow considerable uterine involution before the application of radium.

In the third trimester of pregnancy, there is always a temptation to delay treatment until a viable child can be obtained. Irradiation during that period of delay may injure fetal tissues. Few data are available on the damage that may result. Radioactive gold has been injected into the paracervical and parametrial tissues in a few instances with promising results. Dispersion of gold particles through the lymphatic vessels may irradiate points of tumor spread and contribute a reasonable dose to the cervix without an excessive amount falling on the fetus. Whatever method is followed, the uterus must be emptied by cesarean section. In most clinical reports, the definite treatment has been radical hysterectomy. It is possible that the lower survival rate is partly due to technical difficulties encountered at the time of section, but, since statistical results

for irradiation are also below average, it seems probable that cervical cancer in the latter stage of pregnancy is more apt to disseminate. Large numbers of patients are not to be found, but from the data available one cannot escape the suspicion that irradiation has not yet had an adequate trial in those patients.

### *Residual and/or Recurrent Tumors*

The most difficult therapeutic problem to be met is the management of reappearing or persistent tumors. We may be inclined to describe such tumors as recurrent, but for the most part they represent previously unrecognized residual tumors. Diagnosis is accompanied or followed by intolerable sequelae of terminal stages, including pain, edema, infection, fistula, uremia and progressive malnutrition. Postoperative complications include disturbed anatomy, altered vascularity, fibrosis, and bowel adhesions that make the use of irradiation both hazardous and ineffectual. Postradiation cancer is equally unresponsive due to radioresistance, which is demonstrated by tumor survival following the primary treatment. Fricke and Van Herik have presented one of the few reports on results of irradiation treatment of persistent cervical cancer, and they show a remarkable five year survival rate of about 16 per cent. That result is considerably better than any we have attained, if patients incompletely or partially treated elsewhere are deleted from the series.

Pelvic exenteration, on the other hand, may increase the rate of survival. For a period of almost five years that procedure, in our group, has been under the jurisdiction of Drs. Bricker and Butcher. There is evidence of improvement in rate of tumor control, as well as in palliative relief of sequelae of advanced disease. There remains, nevertheless, a substantial number of patients for whom nothing can be done beyond sedation, chordotomy or lobotomy. Those cases tax beyond anything else the patience and ingenuity of the physician.

To state frankly and conscientiously that nothing more can be done serves only to drive the patient and her family to other sources of advice that often seize unscrupulously the opportunity for exploitation. Final result is resentment against the physician. It is not to be implied that full and detailed knowledge of the serious situation should be withheld from responsible members of the family, because discussion of the problem will rally these individuals to intelligent support of the patient and physician. From that point one should utilize defensive mechanisms supplied by nature. Dehydration and cachexia produce sedative effects. Forcing food and fluids becomes unimportant. Chronic uremia produces a sense of well-being through intoxication. The patient can be told to expect long invalidism, but at each visit the physician should close his interview with emphasis on some small item which is better that day than on previous occasions.

Due to the frequency with which irradiation and radium therapy are useful in gynecology, a discussion of therapeutic problems would be incomplete without mentioning the care required for irradiation reactions. Proximity of the uterus to the bladder and the rectum results in substantial amounts of irradiation falling on those adjacent structures. Tolerance of the bowel is somewhat less than that of the bladder. Proctitis immediately after irradiation is the most common therapeutic problem to be met. Instillation of ½ to 1 oz. of cod liver oil into the rectum each night will provide considerable relief. Other oils tend to macerate the mucosa. Cornstarch enemas of small volume (2 teaspoonfuls of cornstarch in 1 pint of water) taken every other day contribute to relief. Bladder irritations are lessened by forcing fluids and administering alkaline preparations containing Hyoscyamus or similar substances.

The patient should be instructed to continue indefinitely the use of vaginal douches each day, attempting at each irrigation to break up any adherence of the walls. Adequate nutrition should be maintained with supplementary addition of vitamins, iron and protein as indicated.

In conclusion, it should be noted that all complications can be kept at a minimum and better clinical results obtained if treatment of the lesion is given with a maximum of attention to detail and precision.

# Radioactive Isotopes in the Treatment of Cancer

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RADIOACTIVITY has been utilized in medical practice almost since its discovery, but during the past 15 years there has been a great surge of interest in new applications thereof throughout all medical fields. This renaissance of the use of radioactivity was initiated by the availability of cyclotron-produced isotopes and was further stimulated a few years later by the discovery of nuclear reactors from which relatively copious amounts and great varieties of radioactive substances could be obtained.

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F. G. BLOEDORN

It is the purpose of this review to list those applications which have been sufficiently studied to permit appraisal of their usefulness to the practicing physician, either in his own hands or through the referral of patients to an especially equipped center.

A few words should first be devoted, however, to a discussion of the nature of radioactivity, the manner in which radioisotopes are produced, and what their properties are. Almost all of the radioisotopes now used in medicine are obtained either by neutron bombardment of substances placed in a nuclear reactor or by chemical separation of the isotopes arising from fission of the reactor "fuel." After purification, which involves not only the removal of other elements, but also separation from other isotopes of the same element, the materials are ready for medical usage.

There is great variation in the type and

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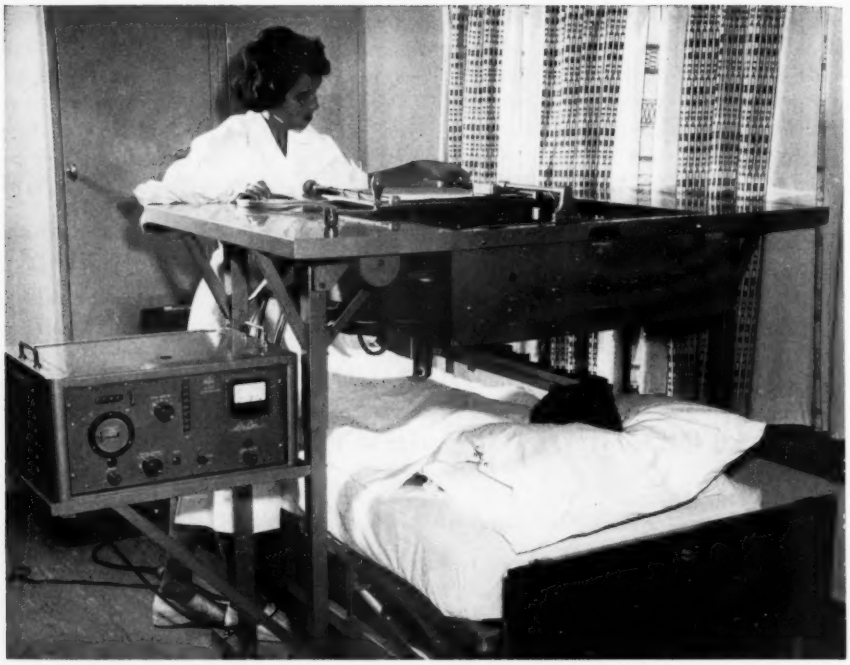

FIGURE 1. The Scintiscanner, an automatic, recording scintillation counter which can be used to measure the distribution of radioisotopes in organs or body cavities.

energy of the radiation emitted by radioisotopes, and there is an even greater range of difference in the time during which such radiation is produced (half-life). The total amount of radiation delivered to tissues which are made to contain these substances is a function not only of the concentration, but also of the energy (which largely determines the range of particles) and of the half-life of the isotope. If the substance is removed by circulating body fluid, either before or after participation in some metabolic process, this factor also affects the number of roentgens finally delivered. For a fuller consideration of the production, properties and dosage of radioisotopes, the reader is referred to "A Manual of Artificial Radioisotope Therapy," by Hahn.

### *Tracers; Metabolically Delivered Isotopes*

It would appear to be a safe assertion that the greatest contribution to medical practice ultimately will be the application of radioisotopes as metabolic tracers in solving problems of fundamental biochemistry. Already thousands of publications have appeared in which important disclosures in this field have been made. The interested reader need only peruse any recent issues of the *Journal of Biological Chemistry* to embark on a fascinating trail of isotope-facilitated investigation and to deduce for himself what may be anticipated in the way of improved prevention and treatment of all types of disease.

The evaluation of the functional state of the normal thyroid gland or the thyroid in any of its diseased conditions has been revolutionized by the use of several of the radioisotopes of iodine ($I^{130}$, $I^{131}$, $I^{132}$) (figures 1 to 4). Most of the significant advances in this field have been recorded in the "Transactions of the American Goiter Association" of the last 10 years. Many of the diagnostic procedures are now so well standardized that the Atomic Energy Commission will authorize the

limited use of $I^{131}$ in the private practice of those physicians who wish to qualify themselves to use this radioisotope and to equip their offices with the necessary devices. Radioiodine has also proved useful in numerous nonthyroidal applications, such as the labeling of proteins which can be used in measuring blood volume or in delineating tumors of the central nervous system.

Therapeutically, $I^{131}$ is of undeniable value in the treatment of hyperthyroidism. There are still two schools of thought regarding the propriety of using this agent in all cases of this disease. However, as more time goes by without evidence of latent harmful effects, much of the entirely justified reluctance of the early days is vanishing. This does not mean that the thyroid surgeon is destined to fade away. There will always be situations in which radioiodine should not be used (pregnancy), but also in which it would be of no value (undifferentiated cancer of the thyroid), or, worse, in which it would be inappropriate treatment (nodular goiters) and serve only to make diagnosis more difficult or to confer a false sense of security on physician and patient alike.

Radiophosphorus ($P^{32}$) lacks the selective localization of radioiodine, but has proved very helpful in the temporary control of some neoplastic diseases (especially chronic myelogenous leukemia and polycythemia vera). While it tends to be somewhat more concentrated in rapidly growing tissues, it is nevertheless so ubiquitous that lethal doses of radiation cannot be delivered to neoplastic cells without exceeding safe limits for normal tissues; hence, hope of destroying tumor cells is always limited.

Radioiodine and radiophosphorus are the two leading examples of guided or "homing" missiles in isotope therapy. Their localization depends on their properties as chemical elements. They may, however, be attached, as may other radioisotopes, to larger, more complex units such as antibodies or protein hormones which themselves are concentrated by specific tissues. Since the ability to deliver ionizing radiation is not affected by mere molecular combination, selective destruction of unwanted cells may thereby yet be achieved in a number of diseases. However, most of the current progress in isotope therapy is in other fields, and the balance of this discussion will be devoted to these (mechanical deposition and teletherapy).

### *Intracavitary or Interstitial Radiation with Colloidal Radioisotopes*

A radioisotope that produces a short-range type of radiation is introduced directly into the place it is needed, either into tumor tissue itself or into a cavity involved by tumor. To qualify for this usage an isotope should meet the following requirements:

1. It should be neither toxic nor caustic to tissues.

2. It should diffuse through organic fluids but not through organic membranes. This assures that the radiation will be delivered uniformly throughout a cavity, but not beyond.

3. If possible, the isotope should produce only radiation of short range, in order to avoid unnecessary damage to normal tissues.

4. The half-life should be neither too short nor too long. Thus far, radioactive colloidal gold, which has a half-life of 2.7 days, has been most widely used in this manner. Its radiation consists of about 90 per cent beta rays and 10 per cent gamma rays. The range of the beta rays in tissue is up to 3 mm. Colloids containing radiophosphorus have also been used in a similar manner.

*Intracavitary radiation*—Intracavitary administration of radioactive colloidal gold may be used in cases in which a pleural effusion or ascites is caused by cancer. In such cases, this procedure is not intended to be curative, but it is a valuable aid in controlling some of the symptoms of patients with incurable cancer. The procedure is simple, and it is harmless when properly used. Unless the physical condition of the patient is extremely poor, the procedure may be used in any case in which a malignant lesion causes a pleural effusion or ascites.

From 100 to 150 mc. of the colloidal isotope may be used. After the fluid has been evacuated, this dose is injected into the pleural or peritoneal cavity. This is followed by

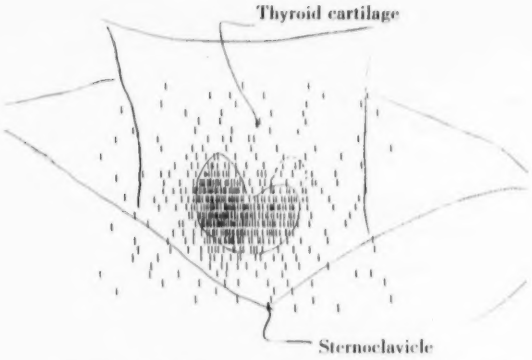


FIGURE 2a. Scintigram made preoperatively in case of metastatic cancer of the lymph nodes of the neck in which the patient was a 42 year old man. Origin of the primary cancer was not known after histologic examination. Palpation did not reveal any abnormality of the thyroid gland. The scintigram, however, shows evidence of nonfunctioning tissue in the region of the left upper pole (area enclosed by dotted line). This suggests that undifferentiated tissue has replaced that portion of the gland. Operation disclosed a primary cancer at this site.

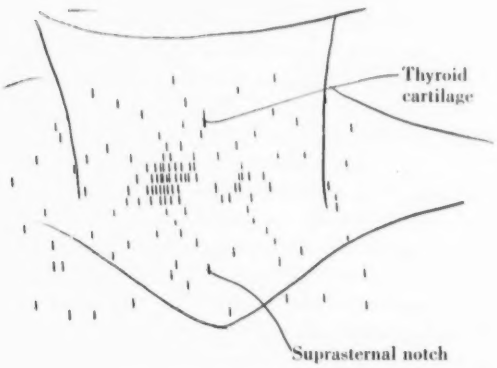


FIGURE 2b. Scintigram made postoperatively in the same case as a. This shows a small amount of residual thyroid tissue, probably in the posterior capsule, although a total thyroidectomy had been performed. Scintigrams frequently call attention to the difficulty of removing all of the thyroid gland.

the injection of about 500 cc. of physiologic salt solution. The position of the patient is changed frequently during the first two hours to insure an even coating of the cavity with the colloidal sol.

The results obtained with this type of treatment have been almost identical in cases of ascites and of pleural effusion. Favorable results have been obtained in more than 70 per cent of cases, and, in approximately 45 per cent of cases, tapping has not been necessary for periods as long as 20 months. The means by which ascites is subsequently alleviated is not understood. No untoward effects are produced if the proper indications for the procedure are observed and if the proper technic is used. The treatment may be repeated as many as three times if needed.

This type of therapy may be used in cases in which ascites is not present provided it is known that malignant cells have been spilled into the peritoneal cavity.

*Interstitial radiation*—In cases of cancer of the prostate gland, the injection of colloidal radioisotopes into the tumor cannot be expected to have any effect on the metastatic lesions. The administration of the isotope in this manner is a simple procedure which can be expected to produce good palliation in a high percentage of cases. No untoward side effects have been observed in about 80 cases of cancer of the prostate in which this method of treatment has been used at the M. D. Anderson Hospital. Approximately 1 mc. of radioactive colloidal gold per gram of tumor tissue has been injected as uniformly as possible into the tumor by a suprapubic cystotomy.

Colloidal radioisotopes also may be injected into parametrial tissues or other tissues involved by a radiosensitive tumor. The use of these colloidal sols has produced promising results in some cases of cancer of the cervix. In these cases, the colloidal isotopes have been used chiefly as supplements to radium therapy or surgical removal of the tumor. The purpose of their use in this manner is to deliver large doses of radiation to the parametrium and the regional lymph nodes.

### *Balloons Filled with Solutions of Radioisotopes*

The use of these balloons has the advantage of perfect control of the time of application, which permits the delivery of a predetermined dose. The most common disease that has been treated in this manner is multiple superficial (papillary) tumors of the bladder.

The results are good provided the method is used only in cases in which extensive, shallow, noninfiltrating tumors are present.

A thin rubber bag is introduced into the bladder and filled with a solution of radiocobalt ($Co^{60}$), radiosodium ($Na^{24}$) or radiobromine ($Br^{82}$). The use of radioisotopes in this manner permits uniform superficial radiation of the entire vesical mucosa.

### *Radium or X-ray Substitutes*

Radioisotopes have an impressive future in the treatment of cancer. Indeed, several already have proved to be exceedingly useful. It is entirely possible that, with the increasing availability of more and newer types of radioisotopes, these will become the principal radiation weapons against cancer within a few years.

The *short-range irradiators (beta ray emitters)* include radiophosphorus ($P^{32}$), radiostrontium ($Sr^{90}$) and radiocerium ($Ce^{144}$). The half-lives of these radioisotopes are as follows: radiophosphorus, 14.3 days; radiostrontium, 20 years; radiocerium, 282 days. These radioisotopes are useful in the treatment of superficial lesions of the skin and benign and malignant lesions of the cornea and conjunctiva.

Blotting paper may be soaked with a solution of radiophosphorus and applied to superficial lesions of the skin. In the treatment of ocular lesions or thin lesions of the skin, radiophosphorus may be mixed with BAKELITE® or thin polyethylene plastic and made into a mold which conforms to the size and shape of the region and lesion to be treated.

Radiostrontium and radiocerium are used in metallic applicators or in thin sheets imbedded in plastic applicators. When used properly in this manner, they produce good results, and they are useful for the treatment of any lesion which is not more than 3 mm. thick and can be benefited by radiation.

In the treatment of deep-seated tumors, *long-range irradiators (gamma ray emitters)* have been used interstitially and by means of a teletherapeutic unit.

The indications for the interstitial use of long-range irradiators are the same as they are for implantation of radium, and the results are similar. If the size and shape of the applicators (needles, tubes, seeds, etc.) are the same as the size and shape of the applicators used for radium or radon, the effect is very similar for the same number of roentgens delivered. The initial cost of these isotopes is less than that of radium, but calculation of the dosage is more complicated because of the more rapid decay of the radioisotopes. Radiocobalt ($Co^{60}$), radiogold ($Au^{198}$) and radiotantalum ($Ta^{182}$) have proved useful when administered interstitially.

Radiocobalt has a half-life of 5.3 years and a gamma energy of 1.25 Mev. It can be

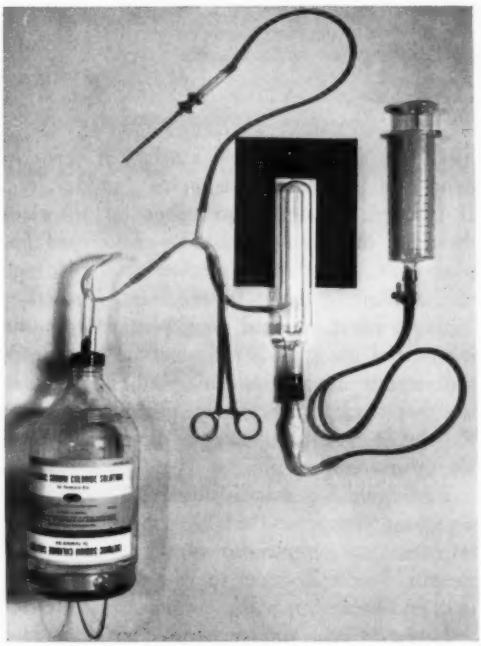

FIGURE 3. Equipment for intracavitary injection of radioactive colloidal gold. After the proper dosage has been determined, a solution of the colloidal radiogold is placed in the siphon which is protected by a lead shield. A three-way tube system permits the injection of radiogold alone, the injection of physiologic salt solution alone, or the passage of physiologic salt solution through the siphon in order to wash the system. A syringe with a three-way stopcock is used to produce either negative or positive pressure in the system. A simple 15 gauge needle is used to evacuate fluid and to inject the radiogold and the physiologic salt solution.

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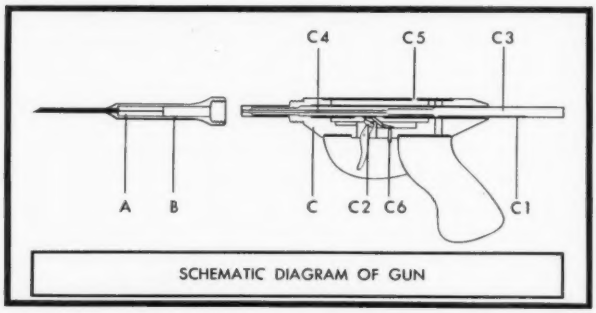


A—Magazine containing radioactive grains. B—Gun barrel with sprung needle. C1—Rack. C2—Pawl. C3—Shaft carrying fine stainless steel ram C4. C5—Hole for seeing number of grains ejected marked on C3.

FIGURE 4a. Diagram of gun devised by Dr. Warren K. Sinclair at the Royal Cancer Hospital in London. The gun is used for the insertion of metallic seeds of radiogold screened by a platinum shield.

(This illustration is published with the permission of Dr. W. K. Sinclair and the *British Journal of Radiology*.)

FIGURE 4b. The gun in actual use for a volume implant on a lesion of the submental region.

used for interstitial implantation in cases of cancer of the skin, oral cavity, bladder, etc. It is used in needles or tubes, or in wires threaded in nylon tubes. The technic of implantation and the calculation of the dosage are similar to those for radium. No better biologic effects should be expected from the interstitial use of this radioisotope than from the similar use of radium. Radiocobalt also has been administered by the intracavitary method in cases of cancer of the uterine cervix or endometrium.

Radiogold has a half-life of 2.72 days and a gamma energy of 0.41 Mev. For interstitial implantation, this radioisotope is placed in metallic seeds. In order to screen out the beta rays and permit only the gamma rays to enter the tumor tissue, the seeds are placed in gold or platinum tubes. The thickness of the walls of the gold tubes is 0.3 mm. and that of the walls of the platinum tubes is 0.15 mm. Indications for using these seeds are the same as those for using radon seeds. The dosage also is the same if correction is made for the difference in the half-life. One millicurie of radon is equivalent to 4.8 mc. of radiogold.

Radiotantalum has a half-life of 111 days and a gamma energy of 1.13 Mev. When administered interstitially, it is formed in flexible wires which are 0.2 mm. in diameter. In order to screen out the beta rays, the flexible wires are placed in a sheath of platinum which is 0.1 mm. thick. These wires are easy to implant into such lesions as carcinoma of the bladder and retinoblastoma, and they are easy to remove. They have some advantages over radium needles and radon seeds.

The use of gamma ray emitters in a teletherapeutic unit (telegamma therapy) provides protection from and collimation of the highly active rays. The teletherapeutic unit is employed for beam therapy comparable with that produced by radium bombs and supervoltage x-rays (up to about 3 Mev.). It is used at a source-skin distance of from 50 to 100 cm., and it provides a very good depth dose.

Telegamma therapy has the following advantages over conventional x-ray therapy: (1) The depth dose is better, (2) the radiation is more homogeneous, (3) the absorption of the rays by different tissues is more uniform, (4) less irradiation of the skin is produced by the same depth dose, (5) the maintenance cost is less, and (6) the administration is easier. The disadvantages are: (1) The initial cost is higher, (2) the activity of the gamma ray emitters declines rapidly, and (3) the beam is less well defined.

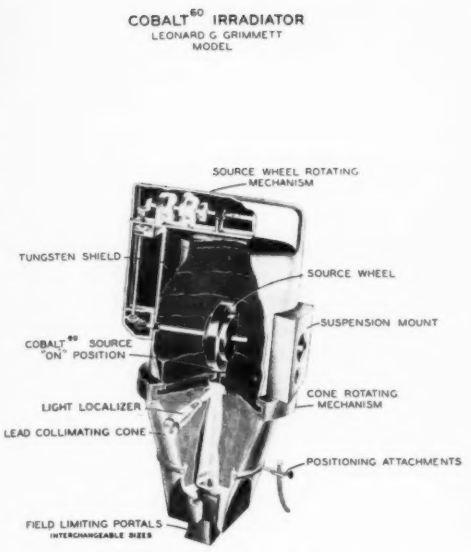


FIGURE 5a. Schematic picture of cobalt bomb in use at the M. D. Anderson Hospital for Cancer Research.

(This illustration is published with the permission of Dr. G. T. Fletcher and *Radiology*.)

FIGURE 5b. The bomb in actual use in the treatment of a squamous cell carcinoma of the tonsil.

The principal indications for telegamma therapy are the same as those for external radiation therapy. It is particularly indicated in the treatment of deep-seated tumors in cases in which skin tolerance limits radiation and in cases in which a thick bone is in the path of the beam.

It is probable that in the near future the applicability of this type of therapy will be broadened by the use of isotopes of different energies of gamma rays, and that it possibly will largely replace x-ray therapy. Thus far, the bombs used in clinical work have contained radiocobalt with the strength of about 1 kilocurie (1000 curies), which is equivalent to $\pm$ 1.6 kg. of radium. In contrast to the radium bomb, the cobalt bomb emits much more uniform rays, and the protection problem is simpler. The half-life (5.3 years) compares unfavorably with that of radium (1600 years). This makes calculation of the dosage more complicated, and necessitates frequent (about every three years) replacement or reinforcement of the radiocobalt.

A few other radioisotopes are being studied in order to determine their effectiveness when administered in this manner. These include radiocesium ($Cs^{137}$) and radioeuropium ($Eu^{152}$).

Radiocesium has a half-life of 37 years and a gamma energy of 0.66 Mev. The energy of this radioisotope is less than that of radiocobalt, the radiation is heterogeneous, and the specific activity is less, which necessitates a larger source and thus increases the penumbra of the beam. Since it has a longer half-life than radiocobalt, it probably will be cheaper than this radioisotope. Less protection will be necessary. Its future use in routine clinical work is quite probable.

Radioeuropium has a half-life of 13 years and a gamma energy of 0.3 Mev. This is a rare material which is more expensive than radiocobalt and yields less energetic radiation. Its future use in clinical work is improbable.

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# Radiotherapy in the Management of the Cancer Patient

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SURGERY and irradiation are the only available weapons which can cure cancer. Chemotherapy has been used in the palliative management of cancer in the last decade, but so far has not proved to be a curative agent. After decades of empiricism, radiotherapy has become a scientific discipline with a body of knowledge based on physics, radiobiology and clinical experience.

An increased knowledge of nuclear physics and the constant discoveries of new radioactive isotopes have brought a stream of potential radioactive tools into the fight against cancer. These rapid changes in the field of radiotherapy have resulted in a certain amount of confusion, often due to a poor understanding of the basic principles of the therapeutic use of ionizing radiation and to the overenthusiasm of many workers. The fascinating developments in the field of atomic and nuclear structure and the mastery in transmuting the elements are accompanied by the feeling of magic of the old alchemy, which has emotionally tinged the therapeutic use of radioisotopes in the treatment of cancer.

Corpuscular or wave radiation produces the biologic changes responsible for the damage made in the living cells through the process of ionization. The difference in biologic action between x-rays, gamma rays, multi-mev. rays, and corpuscular radiation of any type and energy is quantitative, and its explanation known. The number of ion pairs and their spatial distribution (ion density) are the determining factors. All living cells are damaged, and the radiocurability of certain types of cancers is made possible by the margin of radiosensitivity between tumor cells and normal supporting structures.

It follows that the ideal type of radiotherapy would be the uptake of an ionizing agent by the tumor cells alone. This ideal is almost

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achieved by the beta emitters, such as radioactive iodine ($I^{131}$), radioactive phosphorus ($P^{32}$) and radioactive gold ($Au^{198}$). A tumor which will selectively absorb those beta emitters can be heavily irradiated without appreciable damage to the surrounding structures. Certain types of thyroid tumors, leukemia and reticuloendothelial tumors have been fairly successfully treated in this manner. The shortcomings are in the spottiness of the uptake, which results in overirradiated and underirradiated areas, and in the fact that very sensitive structures, such as bone marrow, are still too diffusely irradiated.

The next step is to use x-rays or gamma rays in the same way as surgery. Instead of removing en bloc the volume of tissue containing all tumor cells, a cancerocidal dose of ionizing energy is delivered to the same volume. This eradication by the ionizing knife is possible only if the tumor cells are vulnerable; i.e., more radiosensitive than the supporting structures. Needless to say, these tissues have to recover to preserve function, or even sustain life, if they are a part of the vital organs. This relative radiosensitivity is an inherent quality of the different varieties of cancer and the structures which support them, and is not specific of any ionizing agent; the process is always the same, namely, that of ionization. Tumors which are as radioresistant as the surrounding healthy tissues, for instance neurogenic sarcomas or melanomas, are not helped by any radiation therapy.

Physical science has developed a variety of means of delivering ionizing energy: low energy x-rays (45 kv.), used in skin cancers; deep roentgen therapy (200 to 250 kv.); million-volt machines (1 to 2 mev.); cobalt-60 teletherapy (3 mev. equivalent); ultrahard x-rays produced by betatron or linear accelerators, and many gamma ray (x-ray) or beta ray (electron) isotope emitters. This broad spectrum of ionizing tools has increased the range of attack and enabled one to deliver lethal amounts of ionizing energy anywhere in the body regardless of how deeply located the tumor is situated. The limitation of radiation therapy is no longer in the overtaxing of the tolerance of the skin and other intervening structures, but in the tolerance of the vital organs in which the cancer is growing. This limitation is the same whatever voltage or whatever form of interstitial gamma ray or beta ray therapy is used.

It is thus clear that technical advances in the development of higher voltage radiation or in the discovery of new isotopes do not bring any truly revolutionary approach to the treatment of cancer. They are comparable to the advances made in anesthesiology and physiology, which have made it possible to perform more and more radical operations in circumstances which would otherwise result in a prohibitive mortality or morbidity. A successful surgical treatment is possible if the cancer is still localized to a resectable volume of tissue. The same applies to the ionizing knife. Years of radical therapeutic approach have taught that the curability of cancer is a function of its inherent natural history. If the diagnosis is made when the disease is still localized, a cure is possible. If, as is usually the case in cancers of the esophagus or lung, widespread metastasis is present when the disease is discovered, systemic treatment such as chemotherapy can only achieve limited relief.

Radiosensitivity and radiocurability are not identical terms. This is a concept essential in the understanding of the effectiveness of radiation in the treatment of cancer. Tumors such as the lymphomas are very radiosensitive, but rarely radiocurable because they either generalize quickly, or are a generalized disease to begin with. Keratinizing, squamous cell carcinomas, on the other hand, require very high doses of radiation which approach the limit of tolerance of the supporting structures. If, however, the lesions are localized at accessible sites such as the skin, lip, oral cavity, or vault of the vagina, very high doses can be given to small volumes of tissues, and recovery is still possible. When squamous cell carcinomas, as cancer of the esophagus, are deeply situated, one can still deliver high doses to limited volumes by careful cross-firing or rotation technics. However, as the disease becomes more extensive, the volume to be irradiated is of necessity greater, and the tumor dose has to be reduced as the tolerance of the tissues de-

creases. In such a situation irradiation becomes a palliative measure.

Another concept which was quite prevalent during the first three or four decades of radiation therapy was that tumors which could be excised should be treated by surgery, and that irradiation should be reserved for palliation, i.e., temporary arrest of the growth. This concept was based on the lack of knowledge of what radiation could achieve, and on the high mortality and morbidity of radical operation which, accordingly, was reserved only for curative purposes as one was reluctant to use it for palliation only. Nowadays, the feasibility of radical surgery on one hand, and the excellent results of irradiation in certain sites on the other, have changed the fundamental outlook. One feels justified in using the most radical surgical attack in order to secure relief of distressing symptoms. The thoracic surgeon knows that the chances of curing a resectable cancer of the lung or esophagus are small, but the procedure is justified by the great comfort which is often brought to the patient for the rest of his life.

After half a century, the indications for radiotherapy, borne out by extensive clinical experience, are by no means simple. Varying from the truly curative procedure with maximal preservation of function to the modest aim of relieving pain in cases of advanced cancer, the spectrum covered is quite wide and the application of principles varies depending on the site of the lesion. There is in addition a close correlation of radiation and surgery in treating cancer, and the surgeon-radiotherapist team is often essential to the patient's chance for survival with maximal preservation of function and optimal cosmetic results. The acquired mutual experience brings confidence in each other's judgment, and surgery and radiotherapy become complementary, rather than competitive, disciplines.

Radiation or surgery can be used either separately or combined. In some instances, the indication for one or the other is clear. If the cancer is radioresistant, as the neurogenic sarcomas and adenocarcinomas of the gastrointestinal tract, there is no problem since surgery is the sole method of treatment. If the tumor is extremely radiosensitive, and probably a generalized disease from the beginning, such as the lymphomas, radiation is undoubtedly the treatment of choice. When one is dealing with squamous cell carcinomas which are amenable to both radiation and surgery, there are many determining factors in the selection of treatment. These may be summarized as follows:

1. If the tumors are radiosensitive, and in an anatomic site where surgical excision is impossible (e.g., squamous cell carcinomas of the nasopharynx) radiation therapy is obviously the method of treatment.

2. If the indicated surgery is extremely radical, radiation is preferred, except perhaps in highly specialized centers where surgery is performed almost on an experimental basis. Such instances are the so-called pelvic exenterations for late stage 2, stage 3 and stage 4 carcinomas of the cervix.

3. If radiation and surgery yield results which are comparable on a cure rate basis, the choice is elective and several factors have to be considered. When equally good radiation and surgical technics are available, preservation of function and/or cosmetic results may be the determining factor. However, mutual experience of the surgeon-radiotherapist team, and adequate patient follow-up are a vital part of treatment, since recurrence after use of one of the two methods may be effectively dealt with by the other. Early tumors of the vocal cord are a good example. A laryngectomy is highly curative, but radiotherapy yields a comparable cure rate. If there is residual or recurrent disease, a laryngectomy can still be performed. In this way, the patient has lost neither his chance for survival nor his chance for the preservation of a most useful function. It must be very strongly stated that this is possible only if good radiotherapy is available, as good surgical treatment is better than poor radiotherapy.

4. In several groups of cancers, radiation or surgery alone yields very poor results. A combination of the two increases the survival rate. Some examples are tumors of the paranasal sinuses, extrinsic tumors of the larynx, or advanced tumors of the oral cavity. The se-

quence of the treatments varies according to the site and extent of the disease. Operation and radiation are also used as complementary methods, one to treat the primary lesion and the other to treat the metastatic lesions of the lymph nodes, as in cancer of the tongue treated by radium implants, and metastatic lesions of the nodes of the neck treated by radical neck dissection. In cases of breast cancer, surgery removes the primary lesion and the axillary nodes, and radiation treats the nodes of the apex of the axilla, in the supraclavicular region, in the upper mediastinum and internal mammary chain, all of which are inaccessible by moderately radical surgery.

In addition to these indications, which are curative in their intent, radiation is used as a palliative agent to relieve definite symptoms, such as obstruction of the lumen of the esophagus. It may be used merely to arrest the growth of a tumor temporarily, or to alleviate pain. In this very useful palliative purpose, it must be remembered that clinical judgment is just as essential as in the curative procedures. Ionizing radiation is highly toxic and damaging and should never be used without a specific purpose. Often, the patient is in worse condition after an ill-advised course of radiotherapy than he would be in had he not been treated. Radiation necrosis superimposed on growing cancer is more painful than cancer alone. However tempting it is to the physician to do something for the hopeless patient, the greatest kindness is not always to employ aggressive therapy by the indiscriminate use of a highly damaging agent.

### *Cancer of the Lip and Skin of the Head and Neck*

Both operation and irradiation can achieve a very high cure rate in cases of moderately advanced cancer of the lip and skin of the head and neck. The choice is determined by the ease of accomplishing the desired result and also by the skill of the attending physician. The amount of exposure to the sun, the complexion of the skin, and the age and occupation of the patient are factors to be considered. In institutions in which both skillful surgery and irradiation are available, the treatment of choice is determined not only by the cure rate, but also by simplicity of procedure, cosmetic results and, occasionally, by psychologic factors. As a rule, tumors of the eyelid or slope of the nose can be very simply treated with well-administered radiation of low voltage. On the other hand, tumors on the ear or forehead, where the vascularity is poor, are often best treated by surgery. The plastic surgeon or dermatologist or radiotherapist must only remember the fundamental principle of cancer therapy; namely, that very generous treatment should be applied to the area around the visible tumor. As the tumor becomes more advanced, skillful radiation therapy will produce better cosmetic results than surgery.

### *Cancer of the Oral Cavity*

Squamous cell carcinoma of the oral cavity is a serious disease which, if not treated radically when first diagnosed, will be fatal. The patient has one chance for cure, that is, the first. Consequently, there is no minor procedure of use in the treatment of cancers of the oral cavity. If surgery is chosen, it is always of a radical nature; and the volume of tissue which would have to be excised can often be brought to the necessary cancerocidal level of ionizing energy by skillful irradiation, for instance, interstitial gamma ray therapy.

Early tumors of the tongue, floor of the mouth, and buccal mucosa can be treated by irradiation, which will result in a high cure rate and excellent preservation of function. The follow-up is of extreme importance as a recurrence can still be handled by operation (never by irradiation). The teamwork of the radiotherapist and surgeon is essential to offer the best chance for cure with a minimum of disfigurement and crippling. In the more advanced tumors, both radiation and surgery are at times used to attack the primary disease.

Tumors situated in the floor of the mouth or the gums, and which invade the bone, are as a rule best treated with the so-called commando type of operation. It must also be remembered that surgery is often a better palliative agent in eradicating a painful, unsightly, heavily infected tumor. In cases of tumors of this type, we have found that radiation often

adds only necrosis to the existing tumor.

### *Malignant Tumors of the Nasopharynx and Oropharynx*

Malignant tumors of the nasopharynx and oropharynx, such as reticulum cell sarcoma and lympho-epithelioma, may be very radiosensitive, and both the primary tumor and the metastatic tumors of the lymph nodes of the neck often are permanently controlled by irradiation. Unfortunately, metastasis often occurs to distant regions, and the patients often die of spread of the disease beyond the regional lymph nodes in the neck. The more keratinizing squamous cell carcinoma requires a higher dose, but can be controlled by radiation if it is not too extensive. An over-all cure rate of 20 to 25 per cent has been reported in several unselected series of cases.

### *Malignant Tumors of the Nasal Cavity and Paranasal Sinuses*

Surgery or radiation alone has yielded very low cure rates in cases of these tumors. At the M. D. Anderson Hospital and Tumor Institute, we combine both approaches, performing a radical surgical procedure first. This is followed by intracavitary radium therapy or external beam therapy in all cases of squamous cell carcinoma or adenocarcinoma. This very radical treatment has been well tolerated and the preliminary results have been encouraging.

### *Malignant Tumors of the Larynx and Pharynx*

The surgeon-radiotherapist team is of the utmost importance both in the choice of primary treatment and in the use of a combination of surgery and radiation. Early tumors of the vocal cords can be cured by radiation in a high percentage of cases, but the indications must be definite, and the follow-up complete. If recurrent or residual disease becomes evident, a laryngectomy can be performed thereby allowing another chance for cure. Extrinsic tumors of the larynx and of the pyriform sinus have also been most discouraging to handle by either radiation or surgery alone. It is now the program in our institution to perform a panlaryngectomy, even if the procedure is obviously not going to be curative, and to follow this by heavy irradiation to the whole neck. This program, which has been in effect for five years in this institution, has yielded some striking cures.

### *Malignant Tumors of the Parotid Gland*

In cases of frankly malignant tumors of the parotid gland, either adenocarcinoma or squamous cell carcinoma, surgery alone gives a very low cure rate. The addition of radical radiotherapy, either in the form of radium implantation or external beam radiation with telecobalt units, promises to add a chance for cure in cases in which residual disease is left behind by the most radical surgical procedure.

### *Squamous Cell Carcinoma of the Lung and Esophagus*

These tumors have been treated by so-called deep roentgen therapy ever since 200 kv. machines were manufactured in the late 1920's. Being squamous cell carcinomas, they are relatively radiosensitive, and have some margin of vulnerability with surrounding structures. Cancerocidal doses can be delivered if the tumor is localized to a small volume of tissue. If the tumor is more extensive, larger volumes have to be irradiated, and the tumor dose has to be decreased, thereby lessening the chances for destruction of tumor cells. In carcinoma of the esophagus the use of stationary beams or rotation therapy has yielded interesting palliative results and occasional cures. With the development of thoracic surgery, these cancers became surgical problems and now, after 20 years of extensive surgical experience, we have arrived at a better understanding of the disease. Curability is low, irrespective of the radicalism of the procedure, because too often the disease is generalized when definitive therapy is used.

Analysis of the best cure rates with radiation and operation shows a striking parallelism between the one year, three year, and five year survival rates in cases of cancer of the esophagus. It is now known that the natural evolution of the disease determines the fate of the patient. Owing to the advantages of supervolt-

age therapy, and to the discouraging results of surgery, there is again a trend toward irradiation in the treatment of cancer of the esophagus, particularly for those lesions situated in the upper two-thirds. Operation is still the treatment of choice for lesions of the lower third of the esophagus. It should be remembered that radical radiation taxes the biologic economy of the patient heavily, and the choice between radiation and surgery should not be based on the apparent ease of delivering the ionizing energy. The reopening of the lumen of the esophagus can be obtained in 70 to 80 per cent of the cases, but five year cures are rare. Supervoltage radiation does not change fundamentally the chance for survival, since the course of the disease apparently lies in its natural history. Supervoltage radiation is merely an easier and better tolerated method of delivering high doses to the tumor. Extensive clinical investigation will be necessary to determine whether or not supervoltage radiation produces an improvement in palliative results or an increase in the cure rate.

In cases of cancer of the lung, surgery is the treatment of choice, and radical radiation therapy should be reserved for those cases in which the disease is apparently still localized, but inoperable. When the disease is more widespread and obviously incurable, moderate doses can be used to achieve some definite palliation. In cases of anaplastic tumors, involvement of the mediastinal nodes can be kept temporarily under control. Lastly, gentle doses can sometimes be used to relieve pain. A combination of chemotherapy and radiation has not yielded any better results. In cases of infected tumors or tumors in the terminal stage, radiation should be used only with great discrimination for the relief of pain in localized areas.

### *Carcinoma of the Breast*

Despite innumerable studies, there is a great deal of confusion as to the respective places of surgery and radiation in the management of breast carcinomas. Fundamental understanding of the behavior of the disease and also its mode of spread has changed considerably in the last 10 years due to the systematic study of the internal mammary chain and the supraclavicular and mediastinal nodes. It is now evident that the nodes in the axilla represent only a small area of the lymphatic spread. Long-term analysis has also shown that a permanent cure is often impossible when the patient is first seen, and one can only aid in preventing local recurrences. In those cases in which a radical mastectomy is known to secure a high incidence of local cure, radiation therapy is conceived as a complement to the surgical treatment. Radiation is then directed to the nodes of the apex and the axilla, supraclavicular region, upper mediastinum, and the internal mammary chain.

It is now well known that as the size of the tumor increases, there is also increased likelihood of spread of the disease to the skin and axillary nodes as well as of local recurrence. Many attempts have been made to combine radiation and surgery more effectively in order to prevent these local recurrences.

Preoperative or postoperative radiation is a controversial subject. In our institution we use preoperative radiation in cases of more advanced tumors. It is our preliminary impression that the incidence of local recurrence has diminished, and, therefore, the slight increase in morbidity and delayed healing of the wound is worthwhile. If the tumor is inoperable according to the criteria of Haagensen or if operation is technically impossible, radical radiation therapy alone may yield excellent local control of the disease. Recurrent skin nodules on the chest wall and localized bony metastasis are treated best by radiation.

### *Cancer of the Female Genital Tract*

In cases of squamous cell carcinoma of the cervix, modern radiotherapy yields an 80 per cent cure rate for stage 1, 50 to 60 per cent for stage 2, 20 to 30 per cent for stage 3, and an occasional cure for stage 4 lesions. Equal, but no better, results have been obtained by the best radical surgery in stage 1 and early stage 2 lesions. So far, only radiation therapy yields a reasonable salvage rate in late stage 2 and stage 3 lesions. In cases of stage 4 lesions, pelvic exenteration has yielded some appreciable results.

In skillful hands, the incidence of severe radiation complications is less than 5 per cent. After a decade of revival of excellent radical surgery, radiation therapy is still an effective means of treating cancer of the cervix.

In cases of adenocarcinoma of the body of the uterus, radium therapy by the so-called Heyman's packing technic, plus irradiation of the vagina followed by hysterectomy, has yielded a cure rate as high as 80 per cent. The usefulness of this preoperative radiation has been questioned; but, until further clinical studies have been completed, the combination ought to be considered as a classic technic of management.

In cases of carcinoma of the ovary, both surgery and irradiation secure an occasional cure. The prognosis in the individual case will, of course, depend on the natural behavior of the individual ovarian cancer, i.e., its localization at the time of the original treatment. Once the disease has spread to the entire peritoneal cavity, there is no means of securing a cure, and only temporary palliation can be expected. Intraperitoneal injection of radioactive gold is a useful adjunct in the management of malignant ascites.

### *Malignant Tumors of the Male Genital Tract*

Radiation of the lymph nodes along the spermatic artery and the preaortic nodes is now a classic complement to orchiectomy in cases of seminoma of the testes, and cure rates as high as 80 per cent have been claimed. This tumor is radiosensitive and does not require doses which will damage the intestines or the spinal cord. In cases of embryonal carcinoma or teratocarcinoma, a retroperitoneal dissection may be in order, and residual disease may at times be successfully treated with higher doses to localized areas. Many precautions must be taken with these higher doses, as most severe complications can develop later.

### *Malignant Tumors of the Urinary Tract*

In the last decade, radical surgery has almost completely replaced radiation therapy in the treatment of tumors of the urinary bladder. Total cystectomy with lymph node dissection has been tried on a large scale. Although results are not yet conclusive, there is some indication that they are disappointing. It has been found that if the muscularis mucosae is involved the incidence of metastasis to the pelvic nodes and beyond is very high. The handling of the primary disease alone is then obviously inadequate. In such cases, supervoltage radiation may be advantageous. One can deliver high doses to the bladder and lymph node areas with less reaction than with conventional equipment. Some of the results obtained in centers where this form of radiation has been used have been comparable with those of the most radical surgery, and have been obtained without the postoperative complications of total cystectomy.

In cases of early tumor of the bladder in which there is no involvement of the muscularis mucosae, various local means of treatment (fulguration, partial cystectomy, radium or radon seed implantation) have yielded good results. If the site of the tumor is such that partial cystectomy is not feasible, interstitial gamma ray therapy may be the treatment of choice. Recently, use of radioactive bromide for generalized papillomatosis of the bladder has been effective.

In cases of tumor of the glans penis, skillful radiotherapy is often curative if the shaft is not involved, and amputation can be avoided. If the shaft is involved, surgery is preferable. In all instances, surgery ought to be used in the management of inguinal lymph nodes.

### *Lymphoma and Leukemia*

Chemotherapy has shown the most striking advances in the management of patients with lymphoma or leukemia. A variety of chemicals, specific for the different types of leukemia or lymphoma, are now available. Here, the teamwork of the hematologist and the radiotherapist is essential for the management of the patients over a long period of time, during which multiple series of treatments can be used. In the lymphoma group, lymphosarcomas (small cell or reticulum cell) and Hodgkin's disease are best treated with radia-

tion until the disease becomes generalized. Chemicals should be withheld until this point is reached. When the lymphoma is localized, radiation therapy should be of radical nature, as there is evidence that the length of remission increases with more radical treatment.

In the management of leukemia, localized radiation of the spleen is preferable as long as a good response is obtained. When the disease becomes refractory to localized radiation, total body irradiation or radioactive phosphorus is valuable in addition to the chemotherapeutic agents.

### *Malignant Tumors of the Nervous System*

Some tumors of the nervous system (medulloblastomas, sympathicoblastomas, ependymoblastomas and retinoblastomas) are highly radiosensitive. Unfortunately, their tendency to spread widely is high. Although relief of symptoms and remissions are obtained, the cure rate is low. In the so-called glioma group, the usefulness of radiation has never been conclusively demonstrated, irrespective of the radicalism and carefulness of the treatment.

### *Miscellaneous Malignant Tumors*

There are a number of tumors of varying origin, such as Ewing's tumor, hemangio-endotheliomas and myoblastomas, and some nonspecific, unclassified, highly undifferentiated tumors which are radiosensitive and are best treated with radiation. Even grouped together, these tumors are rare and constitute a small fraction of the cancers seen. It is beyond the scope of this survey to enter into the details of their management.

### *Conclusions*

After half a century of development, radiation therapy, like surgery, is a well-established discipline and an indispensable tool in the management of cancer. Its usefulness ranges from curative treatment with excellent preservation of function to the more modest aim of relief of pain in cases of advanced and incurable diseases. It is a highly specialized field, based on a combination of physics and clinical experience. In addition to its usefulness, its historic importance is great, because the use of radiation in cancer therapy has been the most striking example of a physical means applied to biology and clinical medicine. It has added physics as one of the basic sciences of medicine. It has familiarized many of the men of medicine with mathematics, and has brought more exacting scientific rigidity into clinical investigation. If and when the day comes that cancer is treated essentially by biologic or chemical means, the use of ionizing radiation will have been a historic step in the development of an understanding of the biologic world.


# 40th Scientific Assembly of the Interstate Postgraduate Medical Association

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*Milwaukee, Wisconsin, November 14 through 17, 1955*

Complete program available August 1 from the Interstate Postgraduate Medical Association, Gay Building, Madison 3, Wisconsin

# Treatment of Cancer of the Head and Neck

WILLIAM S. MacCOMB

*The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston*

PRIMARY cancer of the head and neck may respond to either operation or radiation. Radiation therapy without the resulting surgical defects is often to be preferred. Secondary cancer, metastatic from head and neck, is essentially a surgical problem. Thus, both modalities are often necessary in treating an individual patient.

WILLIAM S. MACCOMB

Emphasis must be placed on early and adequate treatment by the chosen method. Whether irradiation or operation is the treatment of choice, the one that is selected should be sufficiently radical to eradicate the disease during initial treatment. Subsequent efforts are handicapped by previous inadequate treatment whether by operation or radiation.

Treatment of the primary lesion may be provided by any of three methods: radiation therapy, operation, or a combination thereof.

### *Radiation Therapy*

Many small lesions of the skin respond well to radiation therapy which may be the treatment of choice if the patient is able to avoid subsequent exposure to the sun and wind.

Intra-oral cancer in most instances is treated effectively by irradiation when the underlying bone is not invaded. Lesions of the tongue, the floor of the mouth, the soft palate, and the buccal mucosa are among those which are treated with excellent results by means of irradiation. Cancer of the nasopharynx is always a radiologic problem; external radiation therapy given over a period of several weeks is the treatment of choice. The cervical regions on each side must be included. Early lesions which are limited to the vocal cords respond effectively to a well-planned course of external radiation therapy. Not only is the cancer cured, but the functional result in the larynx is excellent.

### *Surgical Treatment*

Extensive cancer of the skin should be excised. Repair should be accomplished by any

one of various types of skin grafts. Cancer of the external nose and ear is almost always a surgical problem. Repair is to be effected by plastic surgery. Cancer of the lower lip can be cured by surgical removal, and the resulting defect can be repaired at the same time. The plastic procedure may be accomplished by means of an Estlander or a Bernard triangle, single or bilateral, or a combination of the two triangles may be utilized.

Cancer of the lower gum, often with early bone invasion, is a surgical problem requiring a radical dissection of the neck and a partial resection of the jaw. Any reparative procedure of the resected bone should not be considered until at least six months have elapsed without evidence of recurrent disease.

Cancer of the upper gum or the hard palate, which is prone to involve bone early, should be treated by operation. Resulting defects are closed quite satisfactorily by a dental prosthesis, which permits the patient to eat and to talk in a normal manner.

Cancer of the thyroid, of whatever histologic structure, is a surgical problem. A total thyroidectomy is indicated with a radical neck dissection, bilateral if necessary, when nodes are present which have been proved to be positive histologically.

Cancer of the salivary glands should be treated by operation. Carcinoma of the parotid gland requires a radical dissection of the neck and parotidectomy. If possible, the facial nerve should be preserved.

### *Radiation Therapy and Operation*

There are two methods of combining these modalities: (1) radiation therapy preceding operation, and (2) operation preceding radiation therapy.

*Radiation therapy preceding operation*—Cancer of the posterior third of the tongue, retromolar trigone or pharynx often can be controlled entirely by irradiation. Therapy may be instituted by a combination of interstitial (low-intensity radium needles) and external radiation in order to obtain a satisfactory distribution of the radiation with a desired tumor dose at the center of the irradiated field. If, after a period of two to three months, activity of the cancer is still present, as evidenced by a biopsy, operation should be undertaken. The operation must consist of a radical dissection of the neck, partial removal of the mandible, and excision of the primary tumor. Healing may be delayed after a full course of radiation has been given. The greatest hazard lies in the possible exposure of the carotid bulb by necrosis of the edges of the overlying skin flaps. Repair by a pedicle skin flap from the posterior cervical and occipital regions may be necessary.

The surgical procedure following radiation therapy for cancer of the intra-oral cavity or pharynx requires less extensive removal of the tissues at the primary site of the disease since marked regression from the radiation will have already taken place. The deformity of the face and mouth is then less marked than it would have been if operation had been undertaken primarily. Cosmetically and functionally, and perhaps even economically, the results are better.

*Operation preceding radiation therapy*—Cancer of the paranasal sinuses develops in closed bony spaces. The disease is usually well advanced before biopsy is performed. Obstruction of the air passages causes infection early in the course of the disease, and obscures the true picture and delays the diagnosis. As the cancer grows, the retention of secretions becomes greater and increases the infection. Radiation produces edema of the mucous membranes and an increase in symptoms with little regression of the tumor. Operation consisting of a radical resection of the maxilla, curettage of the ethmoid cells and sphenoid sinuses with exenteration of the orbit, if necessary, is the treatment of choice. If the pathologic report of the biopsy is adenocarcinoma or muco-epidermoid carcinoma, the eye may sometimes be preserved. Most often, however, the microscopic examination reveals squamous or epidermoid carcinoma. The orbit should then be exenterated, thereby increasing materially the possibility of controlling the disease.

Radiation therapy which will deliver a full tumor dose of radiation to the required area may be effectively administered, either by external means or by intracavitary radiation,

the radioactive source (radium or radioactive cobalt) being mounted on an applicator for contact radiation. The large surgical defect consisting of orbital cavity and maxillary sinus together with the nasal cavity of the affected side and including the intra-oral cavity, can be kept clean and may be readily examined for possible recurrence of the cancer. The major portion of the defect is closed off from the intra-oral cavity by a dental prosthesis. The patient is quite comfortable, and the possibility of control of disease is better than it would be if either operation or radiation therapy had been used alone.

The mortality rate of extrinsic carcinoma of the larynx is quite high regardless of the method of treatment. Metastasis to cervical nodes will occur early. If metastasis has already occurred, total laryngectomy with radical dissection of the neck, followed by bilateral external irradiation, is the treatment of choice. If metastasis has occurred on both sides of the neck, a bilateral radical dissection of the neck and total laryngectomy should be performed in one stage.

Intrinsic carcinoma of the larynx which has extended beyond the vocal cord to involve either the subglottic area, the ventricle and lateral wall of the larynx, or both vocal cords should also be considered as suitable for total laryngectomy with postoperative radiation.

Metastatic carcinoma of the cervical lymph nodes which is secondary to a primary lesion of the nasopharynx is sensitive to radiation and responds well to a prolonged course of therapy. Metastatic involvement of the lymph nodes by intra-oral lesions is best treated by a radical dissection of the neck. In cases of extensive metastatic cervical cancer, postoperative irradiation may be of value. If the metastatic disease is not too extensive, most of the nodes involved by lesions of the pharynx and posterior intra-oral region also respond to radiation therapy. These nodes customarily lie within the beam of radiation directed toward the primary lesion. If, in a period of two to three months after the course of radiation has been completed, the enlarged nodes are still present and are proved to be carcinomatous by means of aspiration biopsy, a radical dissection of the neck should be performed. If the presence of metastatic involvement of a node cannot be proved by aspiration biopsy but the clinical findings suggest the presence of such involvement, the node should be excised through a small incision. This is done in the operating room. Examination of a frozen section will determine the final decision as to whether or not a radical dissection of the neck should be carried out. The major operative procedure should be done immediately on receiving a positive report from the pathologist.

A tracheostomy is necessary in performing a combined operation on the neck and jaw, and in a bilateral dissection of the neck. If there is any doubt as to the patency of the airway, a tracheotomy tube should be inserted.

### *Conclusions*

The treatment of cancer of the head and neck is surgical and/or radiologic. At times both types of treatment may be necessary in order to obtain the best possible result. No other method of treating cancer has as yet been discovered. Therefore, if the present-day statistics are to be improved, the best surgical and radiation measures available should be utilized. Inadequate treatment by either operation or radiation reduces the possibility of subsequent control of the disease. The initial treatment of cancer is the most important and the one most likely to produce a cure.

*Scientific Exhibit*

# Gamma-ray Emitting Isotopes vs. Radium

*Departments of Radiology and Physics, The University of Texas, M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston, Texas*

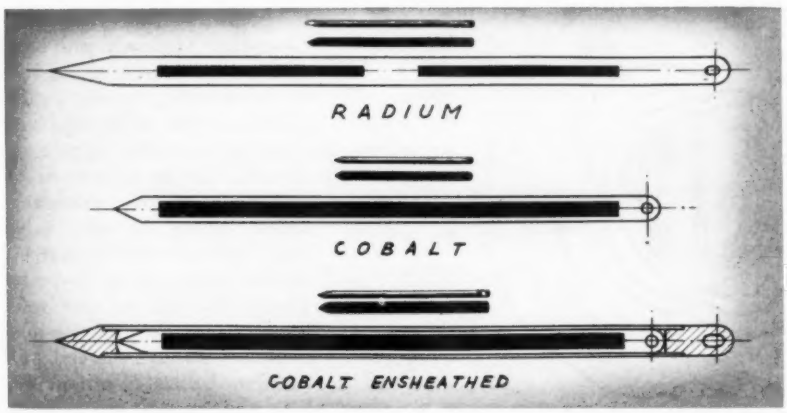
• • •

## Cobalt-60

| | |
|---|---|
| $\gamma$ rays | 1.25 mev. |
| Half-life | 5.3 years |
| Dose rate from 1 mc. (megacycle) | 13.6 r/hr. at 1 cm. |
| Radium equivalent of 1 mc. | 1.6 mg. |

Although the strength of cobalt$^{60}$ needles used interstitially is adjusted to the appropriate radium equivalent, at close range differences may arise due to different construction of the needles or due to differences in absorption coefficient in the sheath material.

The following data show that real physical differences in dose rate occur at close range and that these lead to greater clinical reaction in the case of cobalt$^{60}$ needles.



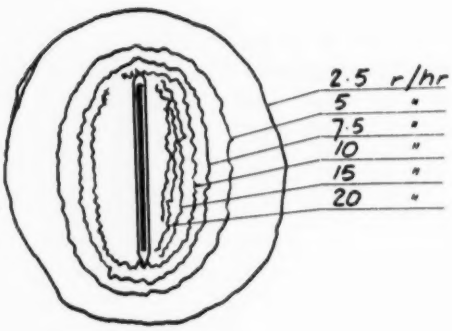

*Top,* Standard radium, cell-loaded platinum-sheathed needles, as commercially manufactured.

*Center,* Cobalt, continuously-filled steel-sheathed 16-gauge needles, as issued by the El Dorado Company.

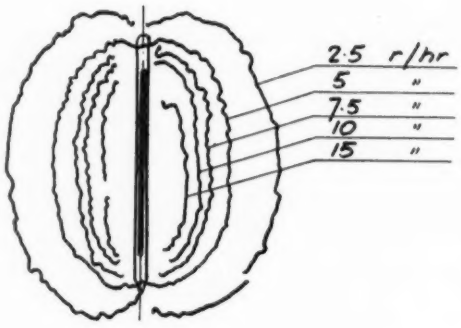
*Bottom,* Cobalt needles enclosed in an extra sheath to give the same length as the radium needles and slightly greater diameter (2.1 mm. compared with 1.83 mm.).

## SOURCES

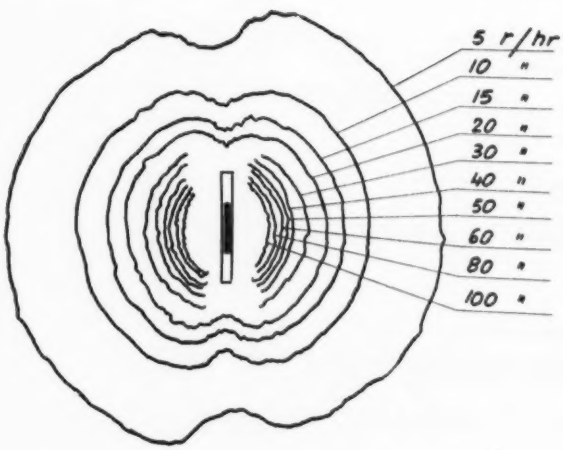
Isodose curves around typical radium and cobalt sources are illustrated. The effects of including a tungsten button in the sheath design are indicated, and the desirability of such an inclusion in cobalt sources intended for use in vaginal applicators is suggested.




Cobalt[60] source, 2 mg. radium equivalent, 3.0 cm. active length, 3.4 cm. over-all length.

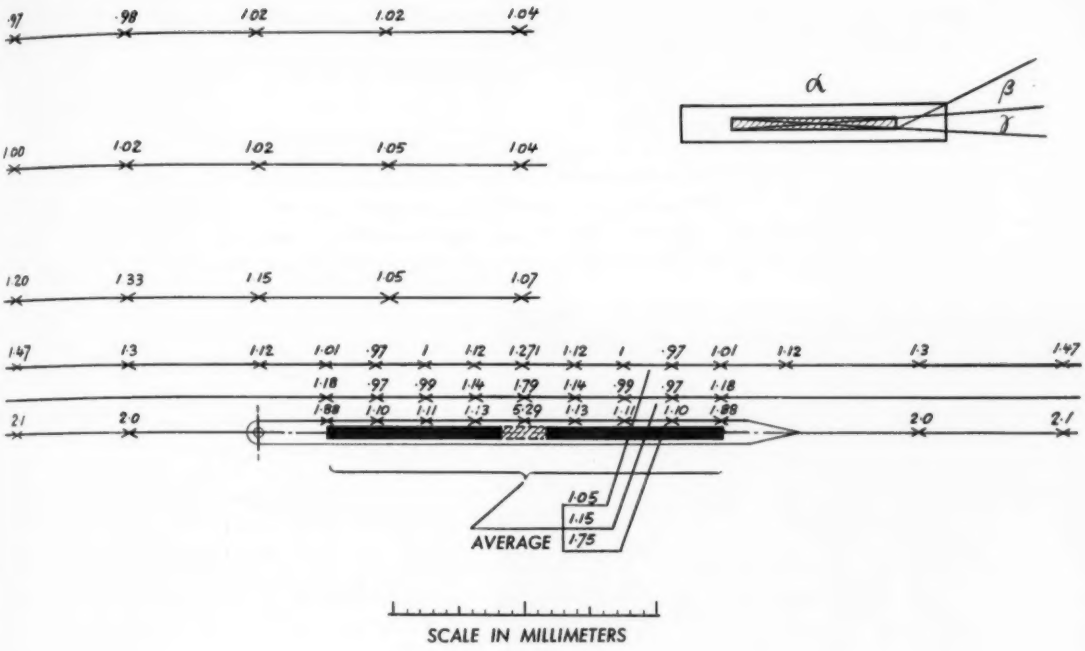



Radium source, 2 mg., 3.0 cm. active length, 4.2 cm. over-all length.




Cobalt[60] source, steel-sheathed, 1.0 cm. active length, 2.4 cm. over-all length, 4.8 mm. tungsten screening at each end.

The mathematical treatment of the intensity around linear radioactive sources depends on the situation of the point considered relative to the geometry of the source and its sheathing. The area can best be divided into three zones labeled in the drawing: alpha, beta and gamma *(upper right-hand corner of figure, page 503)*. In zone alpha, filtration can be considered to be through a cylinder extending to infinity along its axis; in zone beta, only part of the source can be treated in such a way, part is filtered through the end wall of the container; in zone gamma, all is filtered through the end wall in addition to self-filtration. Zones beta and gamma are difficult to deal with mathematically, because of the problem of simplifying, in a satisfactory fashion, the geometry of the points and eyelets of the sources.




The ratio of dose rates of cobalt to radium for sources delivering identical dose rates at 1 meter are shown in diagrammatic form. Those at 0.25 cm. within the active length of the sources and on the surface of the needles were calculated using formulas justified by results shown in the table below. The surface dose rates are those at the surfaces of the actual needles, 0.91 mm. from the axis in the radium needles, and 0.8 mm. in the cobalt needles; the cell-loading was used in the calculations.

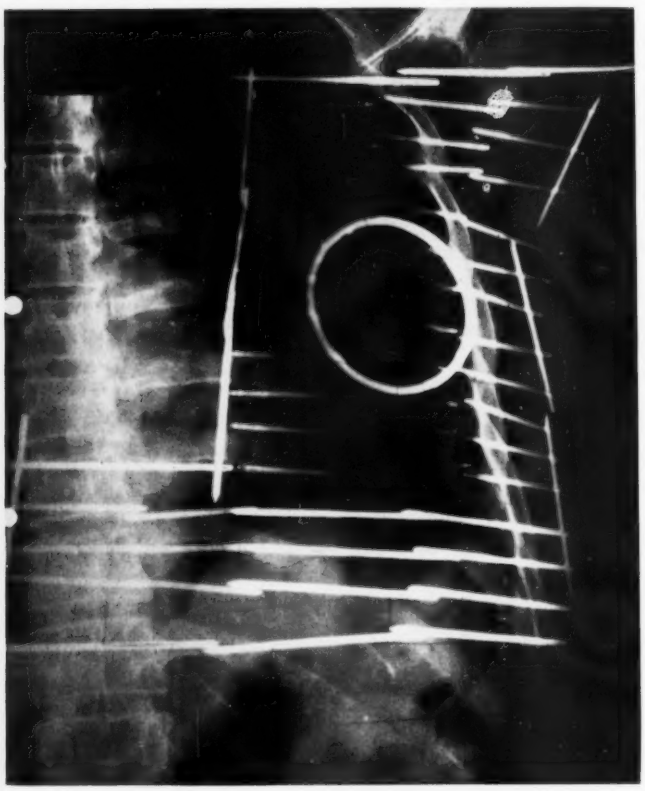
| Isodose Curve | 2.5 r/hr. | 5 r/hr. | 10 r/hr. |
|---|---|---|---|
| Ratio Cobalt to Radium | 1:2 | 1:14 | 1:12 |

The ratio of volume enclosed by the isodose surfaces of 2.5, 5 and 10 r per hour were calculated from the isodose curves, assuming the surfaces to be surfaces of revolution of these curves. The results are tabulated above. The largest differences between cobalt and radium occur when the end effects are included in the volumes, e.g. 2.5 r surface.

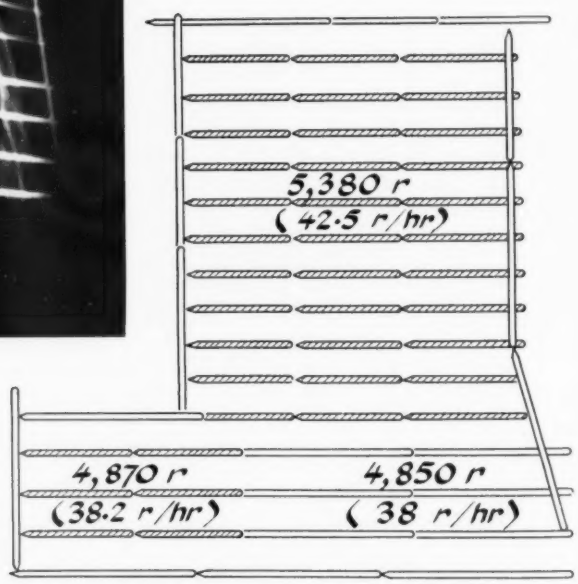
# Clinical Applications

## COBALT

**Single plane implantation of chest wall for recurrent skin nodules following simple mastectomy and previous inadequate irradiation treatment (exact amount of irradiation administered unknown). The axilla, supraclavicular region and internal mammary chain were first treated with roentgen radiation before implantation.**

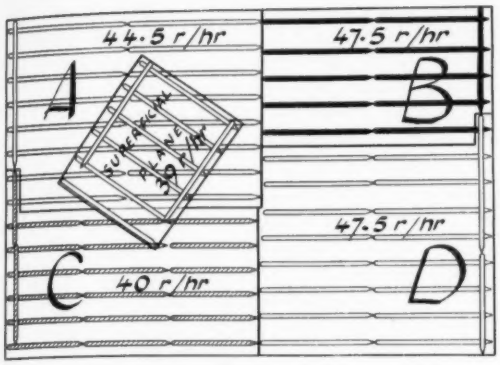


The distribution of radium and cobalt sources (16-gauge) are seen on diagram (B), page 505. Activity of the cobalt sources was within 2 per cent of the equivalent activity of the radium. The dose rates were calculated separately for the larger cobalt area, the radium area and the smaller cobalt area. The small cobalt area and the radium area are suitable for comparison of erythema: same doses, no previous roentgen therapy, located similarly relative to the large area of external irradiation and interstitial implantation.




(Case No. 9423)

= Cobalt$^{60}$, not sheathed
= Radium




(Case No. 9660)

Cobalt$^{60}$, sheathed
Cobalt$^{60}$, not sheathed
Radium

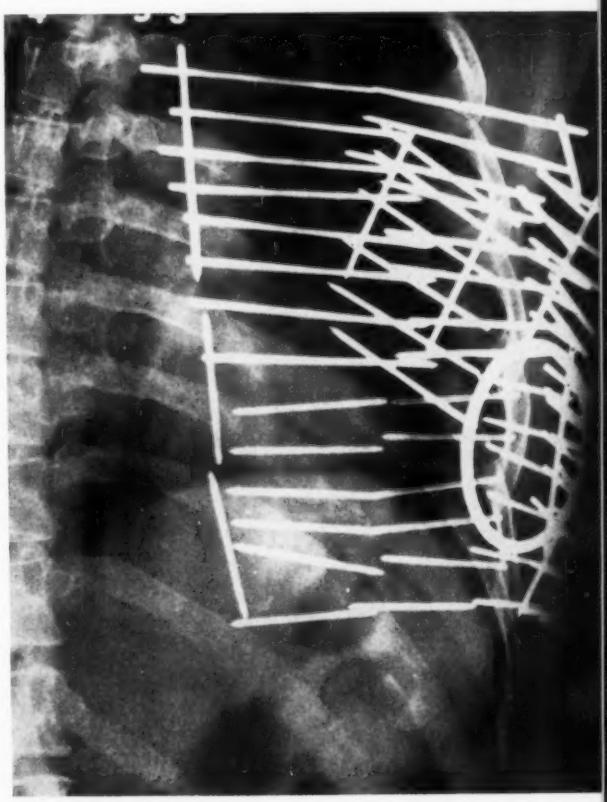
Total dosage in 0.5 cm. plane over all areas: 5500 r
Maximum dosage between superficial plane and area "A": 9,320 r

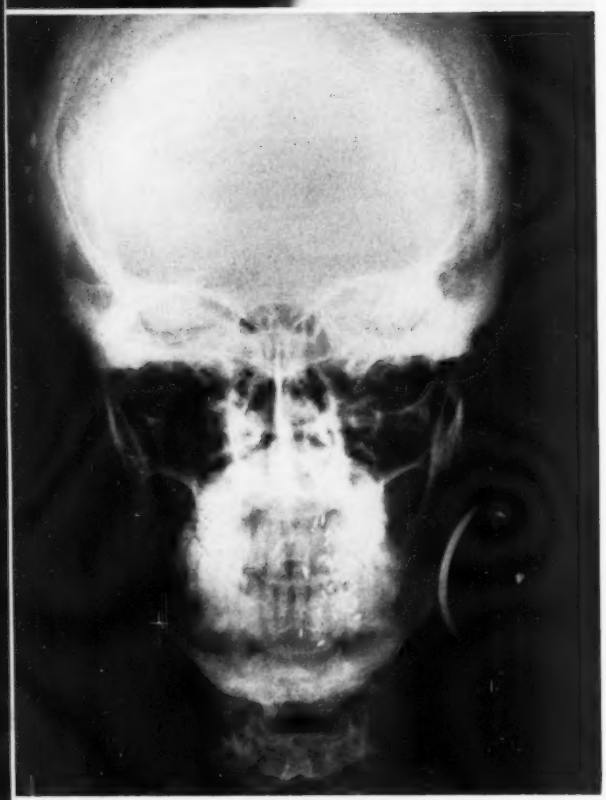
The reactions *(figures on opposite page)* over the cobalt and radium areas differed in two ways. (1) Over the radium area a faint, fast-subsiding erythema was present, with bands of brisker erythema over the needles, showing lack of uniformity of dosage to sensitive layers. A brisk erythema developed over the cobalt area within a week, evolving into partial moist desquamation which healed in four weeks. (2) The holes of entry of the radium needles did not show evidence of acute slough (as is the case if the needle ends have been well buried) and healed rapidly. This was true even for the crossing radium needles implanted at the margin of the internal mammary chain field. On the other hand, large sloughs (up to 0.75 cm. in diameter) developed around the holes of entry of the cobalt needles (C). They were not healed at four weeks.

The greatest reactions *(figures on this page)* remained in the commercial cobalt implant, the skin reaction being greater and necrosis being near sites of entry of needles. Skin reaction with unsheathed cobalt was slightly greater than that of the radium but no necrosis occurred around the sites of entry.

*Fixed, inoperable carcinoma in a small breast*—The chest wall was implanted with a large planar implant reinforced by a superficial plane in the breast itself. The large implant was made of four parts. The dosage rates in the various areas were carefully computed and the needles were removed at different times in order to deliver 5500 gamma roentgens to the large planar implant. The areas B, C and D on the diagram are suitable for comparison.

A stripelike erythema developed over the radium area (D) in contradistinction to a uniform, brisker erythema along the lateral border of areas B and C extended outward in a fading-away fashion while it was limited and sharply defined by the peripheral needles of the radium implant. Moist desquamation was generalized over areas B, C and D but epithelization started earlier and progressed faster over area D. Acute slough developed at the holes of entry of the unsheathed needles (area C). The holes of entry of radium needles and sheathed cobalt needles showed no evidence of radiation slough.





# Gold

Extremely advanced tumor, probably originating in the left tonsillar fossa, which is replaced by a deep crater occupying the entire lateral pharyngeal wall of the oropharynx. The glossopalatine sulcus and more than half of the tongue are involved. The involvement of the tongue reaches almost to the tip and crosses the midline on the base of the tongue. The palate is only slightly involved. A node measuring about 3 cm. in diameter is present behind the left angle of the jaw, and another node measuring 2.5 cm. in diameter is palpable under the sternocleidomastoid muscle at the midjugular level.

A tumor dose of 6000 r was delivered in five weeks by combination of single field cobalt$^{60}$ therapy and a modified pterygoid tongue implant. The neck nodes were also treated. Seven weeks after the completion of treatment there was still an induration measuring about 3 cm. in diameter occupying more than half the base of the tongue and extending anteriorly. A three-dimensional gold pellet implant was the treatment of choice to give irradiation without traumatizing the mucous membrane of the base of the tongue and to decrease the chances of infection and necrosis in view of the previous heavy irradiation.

The implant can be considered as a cylinder.

$$\text{Volume} = \frac{\pi}{4}$$

$$\text{x } 3.95 \text{ x } 1.69 \text{ x } 1.76 = 9.24 \text{ cm.}^3$$

$$302 \text{ mg. hr./1000 r}$$

$$24 \text{ seeds} — 0.81 \text{ mc. each eq. of radon}$$

$$24 \text{ x } 0.81 \text{ x } 133.3 = 2{,}595 \text{ mg. hr.}$$

$$\text{Elongation } \frac{3.95}{1.72} = 2.3 \text{ correction} + 8\%$$

$$302 \text{ x } 1.08 = 326 \text{ mg. hr./1000 r}$$

$$\frac{2{,}595}{326} = 7{,}950 \text{ r}$$

Ten days following the implantation a uniform pseudomembranous mucositis was present over the base of the tongue, the soft palate, the glossopalatine sulcus and the faucial pillars. This uniform reaction was evidence of a successful volume implant.

# Gold-198

| | |
|---|---|
| γ rays | 0.41 mev. |
| Half-life | 2.7 days |
| Dose rate from 1 mc. | 2.42 r/hr. at 1 cm. |
| Radium equivalent of 1 mc. | 0.29 mg. |

Gold[198] has a suitable half-life to simulate radon seed technics and sources can readily be prepared for this use by irradiation in the pile.

## Two Technics Are Used

*Columbus (Ohio) Technic*

Providing gold seeds of adjustable activity which can be conveniently used in single plane implants.

*Royal Cancer Hospital (London) Technic*

Providing magazines of 15 gr. each which can be used with an implantation gun in volume implants.

| | |
|---|---|
| Gold equivalent of 1 mc. of radon | 4.8 mc. |
| Usual activity used | 4.3 mc. |
| Equivalent to | 0.9 mc. radon |
| Irradiation time | 1 week or less |

## Diagnosis

Recurrent basal cell carcinoma of the face, after surgery, x-ray and radium therapy.

## History

Lesion began in the nose 12 years ago. Four years ago, patient underwent surgical removal of large portion of the external nose, and a few months ago x-ray and radium treatment was given. Patient came to the M. D. Anderson Hospital with a large defect, a large portion of frontal bone exposed. Around the left margin of the defect there was an ulceration with tumor actually present.

## Biopsy

Basal cell carcinoma.

## Indication

Further surgery was not possible. A gold seed implant was the only procedure which could *locally control* the disease without risking a dangerous necrosis, due to previous heavy radiation of the area.

An implant of gold seeds (metallic $Au^{198}$ gold screened) was rather empirically inserted where the disease was obvious.

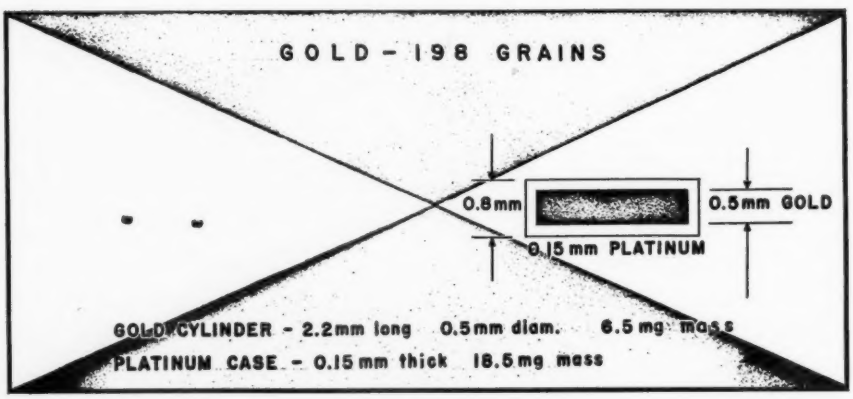
## Calculation

Considered as only approximations, due to the uneven distribution of seeds made necessary by the anatomy of the lesion. It was considered as a single plane pattern.

Area covered by seeds: 7.6 $cm.^2$
22 gold seeds were used, 1 mc. radon equivalent each. From Paterson-Parker tables, 200 mg. hours produce 1000 r at 0.5 cm. from the plane of the implant.

## Comment

Three months later (photo) the disease was controlled on the area so treated without untoward reaction. More disease surrounded the other portion of the surgical defect, which was to be treated with the same technic.


GOLD - 198 GRAINS
0.8mm
0.5mm GOLD
0.15 mm PLATINUM
GOLD CYLINDER - 2.2mm long 0.5mm diam. 6.5 mg mass
PLATINUM CASE - 0.15 mm thick 18.5 mg mass

Infiltrative squamous cell carcinoma measuring 3 cm. in diameter in its greatest dimension located in the floor of the mouth and undersurface of the tongue.
A dose of 7000 r was delivered in 124 hours by a radium volume implant. Four months later a right radical neck dissection was performed for a right submandibular mass. Fifteen months later, a mass measuring 4 cm. in diameter was felt in the submental region fixed to the arch of the mandible. An aspiration biopsy was positive. Due to the location, the attachment to the bone, and the danger of traumatizing and re-irradiating heavily the floor of the mouth, a three-dimensional gold pellet volume implant was the only procedure which could be performed without excessive danger of necrosis.

The volume is an ellipsoid.

$$\text{Volume} = \frac{4}{3} \quad \frac{3.19}{2} \quad \frac{4.8}{2} \quad \frac{5.07}{2} \quad = 40.6 \text{ cm.}^3$$

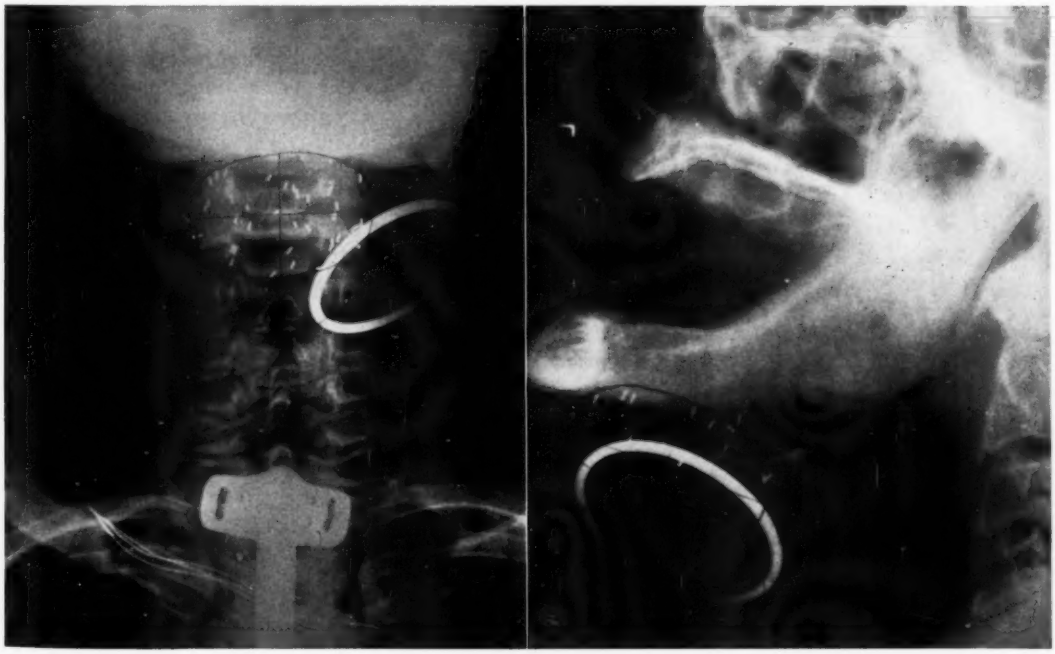
$$624 \text{ mg. hr./1000 r}$$

$$41 \text{ seeds} — 0.85 \text{ mc. eq. of radon each}$$

$$41 \times 0.85 \times 133.3 = 4{,}640 \text{ mg. hrs.}$$

$$\frac{4{,}640}{624} \times 1000 = 7{,}430 \text{ r}$$

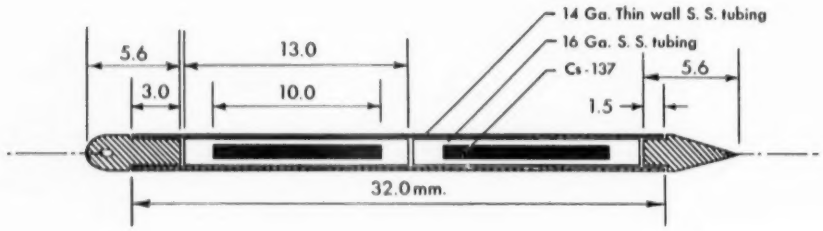
Three weeks after the implant moderate reaction of the mucosa of the floor of the mouth was superimposed on the late chronic changes. Only faint erythema of the skin has been present. The mass has markedly softened.



# Cesium-137

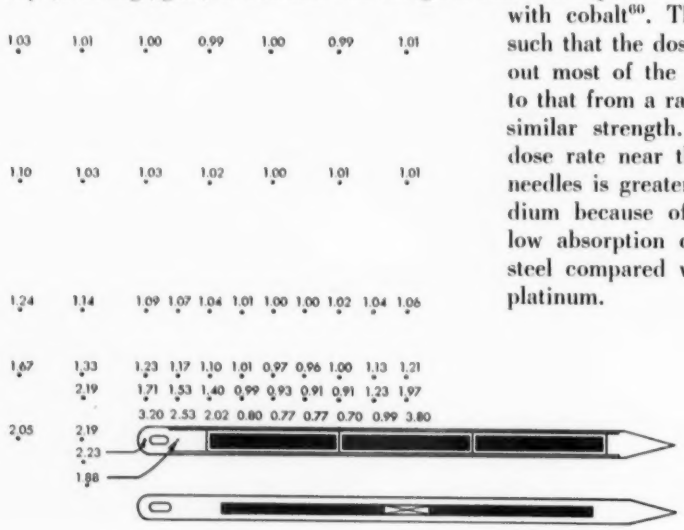
| | |
|---|---|
| $\gamma$ rays | 0.66 mev. |
| Half-life | 37 years |
| Dose rate from 1 mc. | 3.1 r/hr. at 1 cm. |
| Radium equivalent of 1 mc. | 0.37 mg. |

Cesium$^{137}$ has certain advantages as a radioactive material for loading into needles for interstitial purposes. It is available in high specific activity and relatively large quantities from fission products. It has a long half-life, the decay rate for cesium$^{137}$ being only 1.5 per cent per year compared with 1 per cent per month for cobalt$^{60}$. Since cesium is most conveniently available in the form of a salt, cesium sulfate, needles should be prepared in cells similar to radium needles. Experience with cobalt$^{60}$ needles has shown that the dimensions should be carefully studied if the resulting needles are to be comparable with radium in inflexible needle technic.



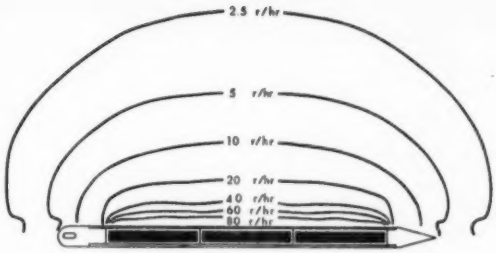

## PROPOSED CESIUM NEEDLE

The diagram below shows a suggested design for needles loaded with three cesium cells, each containing 1.8 mg. of cesium$^{137}$ to duplicate the normal linear intensity (0.66 mg./gm.) of radium. The design is based on experience already gained with cobalt$^{60}$. The diameter is such that the dose rate throughout most of the field is similar to that from a radium needle of similar strength. However, the dose rate near the ends of the needles is greater than from radium because of the relatively low absorption of cesium$^{137}$ in steel compared with radium in platinum.

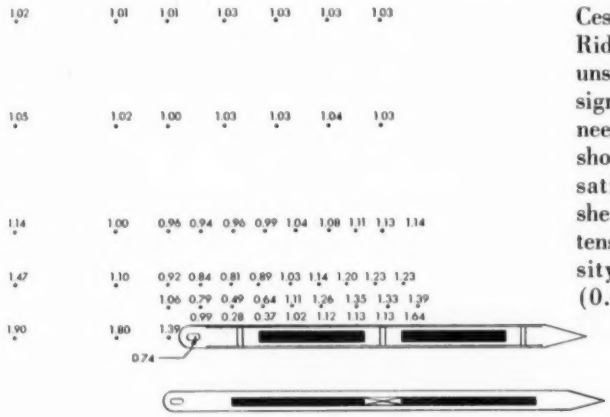


The dose rates about the suggested cesium needle are shown relative to radium for activities which would yield the same dose rate at one meter. The dose rates were calculated using the same method as that already indicated for cobalt$^{60}$.

The ratios found are clearly very close to unity in most cases and it may therefore be concluded that needles of this design would have a reaction very similar to that with radium needles.

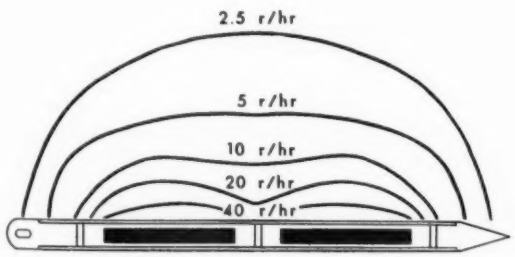



## EXISTING CESIUM NEEDLE




Cesium cells prepared at Oak Ridge had an activity and length unsuitable for the suggested design given above. A "practical" needle was therefore designed as shown in the diagram which has satisfactory "dead ends" and sheath, and the same linear intensity as so-called "half intensity" (0.33 mg./cm. radium) (0.94 mg./gm. cesium). The active length (2.6 cm.) is a little shorter than the length of standard radium needles.

Dose rates relative to radium are shown for the "practical" cesium needle. The dose rates were calculated in the same way as for cobalt$^{60}$ with appropriate adjustments for the difference in active length.



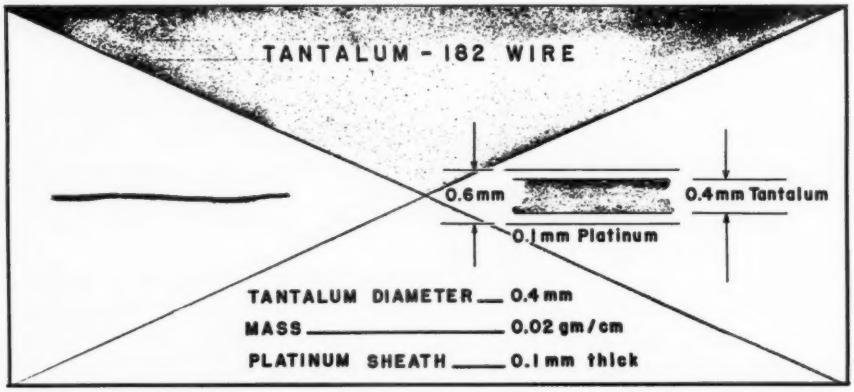
# Tantalum-182

| | |
|---|---|
| $\gamma$ rays | 1.1 mev. |
| Half-life | 111 days |
| Dose rate from 1 mc. | 6.1 r/hr. at 1 cm. |
| Radium equivalent of 1 mc. | 0.73 mg. |

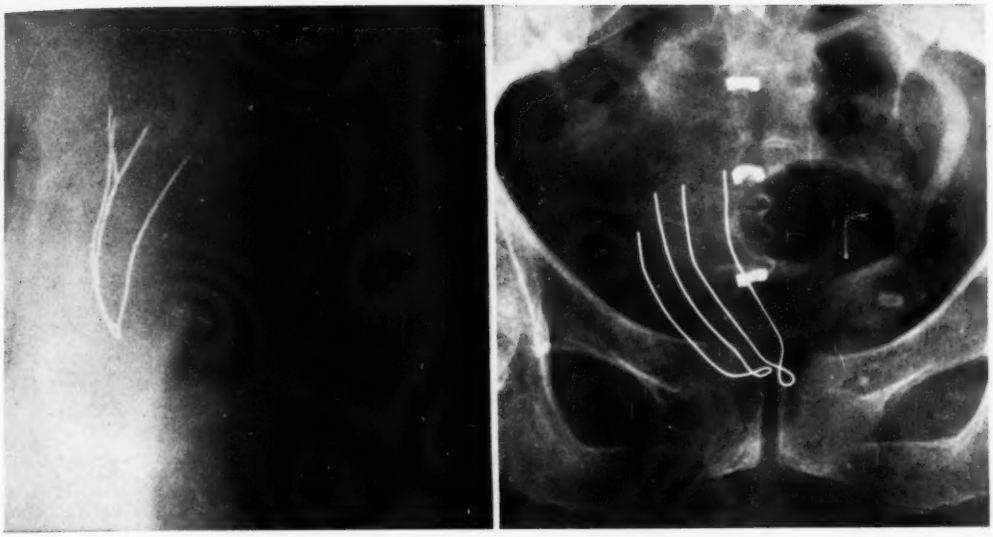
There are clinical circumstances where it is advantageous to have a flexible radioactive source for interstitial implants. These cannot readily be provided by the natural radioactive isotopes and among the artificial isotopes tantalum$^{182}$ appears the most suitable. It is easier to sheath than cobalt wire and tissues exposed to tantalum do not absorb the radioactive material as they do if bare cobalt comes in contact with them. The half-life of tantalum$^{182}$ is sufficiently long compared with the normal treatment time, and also long enough to maintain a stock of wire from which suitable activities can always be drawn. Since the wire is frequently used in clinical circumstances where its repeated use is undesirable (notably in the bladder) its shorter half-life becomes an advantage from a disposal point of view.

| | |
|---|---|
| Usual activity used | 0.9 mc./cm. tantalum$^{182}$ |
| Equivalent to | 0.66 mg./cm. radium |
| Irradiation time | (about 4 weeks at $10^{11}$ neutron/cm.$^2$/sec.) |

## FORK OR HAIRPIN OF TANTALUM WIRE

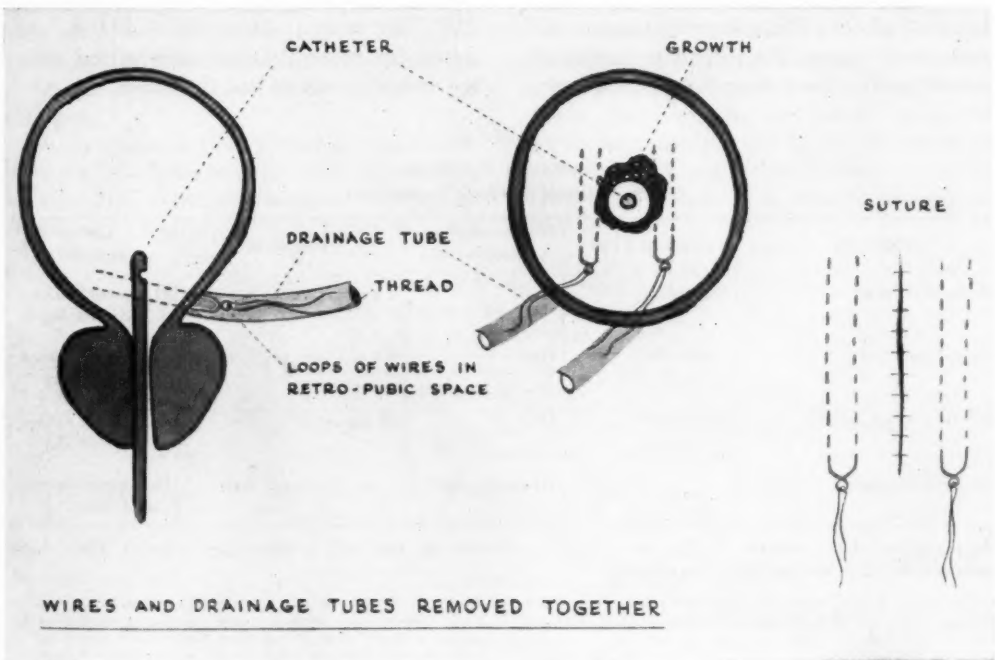



For the interstitial implantation of small tumors of the bladder it is convenient to shape the active tantalum wire in the shape of a fork or hairpin as shown. The wire is looped in its center so that a thread can be attached in order to withdraw the hairpin at the end of the irradiation period. The two arms of the hairpin are about 1 cm. apart and the length is adjusted to suit the size of the tumor. Most often the length of the arms is between 10 and 12 cm. More than one hairpin is used for tumors of greater area. The implants usually deliver a dose of about 7000 r in the 0.5 cm. plane in five to seven days.



This case involved a papillary tumor 4 cm. in diameter, partially pedunculated in the region of the right ureteral orifice. The projecting growth was grasped in papilloma forceps. The base was divided and then sutured. One tantalum hairpin was inserted along each side of the suture line using the special introducer. The wire used had an activity of 0.60 mg. radium equivalent per centimeter and the dose delivered was 5,740 r at 0.5 cm. in 103 hours.

(The case illustrated was treated at the Royal Cancer Hospital [London] and is shown by courtesy of Professor D. W. Smithers, Mr. D. M. Wallace and Dr. N. M. MacKay.)



# Hormonal and Chemical Methods in the Treatment of Cancer

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INOPERABLE and far advanced cancer presents many difficult problems and, while the response of the patient may be uncertain and improvement temporary, the physician should be able and willing to apply the limited therapeutic methods that are available. The hormonal and chemical agents useful in the treatment of cancer are not curative, and they do not control the disease indefinitely. In exerting measurable and predictable effects on certain forms of neoplastic disease, however, they may prolong life, relieve discomfort, and temporarily restore the patient to apparently normal health. These drugs must be used carefully. They are pharmacologically active compounds with serious toxic actions, and they frequently are given to the point of tolerance in an effort to achieve a therapeutic response.

In this brief article tables will be used to show the pharmacologic action of the hormonal and other chemical agents used in the treatment of cancer (tables 1 to 8), and to describe the nature of the clinical response and the indications for these drugs in relation to other therapeutic methods (tables 9 to 21). The medical literature should be consulted for more detailed information about the various products and their uses.

TABLE 1

ESTROGENIC HORMONES

*(Partial List of Available Preparations)*

| COMPOUND | COMMON NAME | ROUTE OF ADMINISTRATION | USUAL DOSE† | ACUTE TOXICITY |
|---|---|---|---|---|
| Diethylstilbestrol | Stilbestrol | Oral | 1 to 5 mg., t.i.d. | Occasional nausea and vomiting |
| Ethinyl estradiol | ESTINYL® | Oral | 0.1 to 1 mg., t.i.d. | Occasional nausea and vomiting |
| Sodium estrone sulfate | PREMARIN® | Oral | 10 mg., t.i.d. | Occasional nausea and vomiting |
| Estradiol benzoate | | Intramuscular | 5 mg., 3 times a week | Occasional nausea and vomiting |

†In carcinoma of the prostate, the dose is one-tenth to one-fifth the dose used in cancer of the breast. These doses represent the high and low doses respectively.

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This paper is based on work which has been supported in part by Grant C1889 from the National Cancer Institute of the National Institutes of Health of the United States Public Health Service and by grants from the American Cancer Society and the Lasker Foundation.

*General toxicity*—The effects of increased estrogenic activity include fluid retention, enlargement of the breasts, and uterine bleeding which usually begins when the administration of the drug is stopped.

*Special precautions*—In impaired cardiac function, fluid retention may lead to heart failure; in osseous lesions from breast cancer, activation of the disease with estrogens may cause or aggravate pre-existent hypercalcemia. If uterine bleeding occurs while estrogen therapy is used, the dose should be increased.

*Mechanism of action*—These drugs possibly act by interfering with pituitary activity, by inhibiting androgenic hormone activity, or by direct action of estrogens, thus producing a hormonal imbalance which may induce regression in hormonally dependent tumors.

*Principles of treatment*—It is desirable, if possible, to give a dose adequate to induce a hormonal imbalance without concomitant, severe physiologic disturbances. Treatment is given for a trial period of two to three months, and continued while the patient is responding. It is stopped when reactivation occurs despite treatment.

TABLE 2

ANDROGENIC HORMONES

*(Partial List of Available Preparations)*

| COMPOUND | COMMON NAME | ROUTE OF ADMINISTRATION | USUAL DOSE | ACUTE TOXICITY |
|---|---|---|---|---|
| Testosterone propionate | | Intramuscular | 50 to 100 mg., 3 times a week | None |
| 17-Methyltestosterone | | Oral | 100 mg. per day | None |
| Dihydrotestosterone | NEODROL® | Intramuscular | 100 mg., 3 times a week | None |

*General toxicity*—The effects of increased androgenic activity include fluid retention and evidence of masculinization, such as hirsutism, lowered pitch of voice and increased libido.

*Special precautions*—Similar to those for estrogens.

*Mechanism of action*—These hormones possibly act by interfering with pituitary activity, by inhibiting estrogenic hormone activity or by a direct androgenic effect, thus producing a hormonal imbalance which may interfere with growth of hormonally dependent tumors.

*Principles of treatment*—It is desirable, if possible, to give a dose adequate to produce a clinical response without excessive virilizing effects. The hormones are usually given for two or three months and their administration continued if the patient is responding satisfactorily. Administration is stopped when a relapse occurs.

TABLE 3

ADRENOCORTICAL HORMONES AND ACTH

*(Partial List of Available Preparations)*

| COMPOUND | COMMON NAME | ROUTE OF ADMINISTRATION | USUAL DOSE | ACUTE TOXICITY |
|---|---|---|---|---|
| 17-Hydroxy-11-dehydrocorticosterone acetate | Cortisone acetate | Oral and intramuscular | 50 to 300 mg. per day in divided doses | None |
| 17-Hydroxycorticosterone acetate | Compound F; hydrocortisone acetate | Oral and intravenous | 50 to 200 mg. per day in divided doses | None |
| Adrenocorticotropic hormone of anterior lobe of pituitary body | ACTH | Intravenous | 25 to 50 mg. per day by continuous infusion | None |
| | | Intramuscular | 10 to 20 mg. every 3 hours | None |

*General toxicity*—The effects of excessive adrenocortical hormone activity, either from exogenous administration or endogenous production of ACTH, include fluid retention, hypertension and coma, diabetes mellitus, moon facies, hirsutism and increased susceptibility to infection.

*Special precautions*—A low salt diet should be used to avoid fluid retention; additional potassium should be given to control hypokalemia, and the dose of the hormone should be decreased if hypertension or coma develops. Particular care should be observed in treating patients who are likely to have mental disturbances or who have a history of duodenal ulcer, diabetes or heart disease. If infection develops after the hormone has been administered for several weeks or longer, the dose usually should be increased temporarily until the infection is controlled.

*Mechanism of action*—Adrenocortical hormones inhibit the growth of certain tissues, particularly those of mesodermal origin. Neoplastic cells with such susceptibility may be temporarily restrained in their growth, but they ultimately become resistant.

*Principles of treatment*—In most cases, if there are no complicating factors, a large dose is given initially in order to give the maximal opportunity for a therapeutic response. If no improvement occurs, the dose may be continued or increased unless serious complications develop; if a satisfactory response occurs, the dose is gradually reduced to the minimal effective dose, or administration may be stopped. ACTH is given in acute situations.

TABLE 4

POLYFUNCTIONAL ALKYLATING AGENTS
*(Nitrogen Mustard and Related Compounds)*

| COMPOUND | COMMON NAME | ROUTE OF ADMINISTRATION | USUAL DOSE | ACUTE TOXICITY |
|---|---|---|---|---|
| Methyl-bis (β-chloroethyl) amine hydrochloride | HN2; nitrogen mustard; MUSTARGEN® hydrochloride | Intravenous | 0.4 mg. per kg. of body weight for a course; administered as a single dose or in divided doses | Nausea and vomiting |
| Triethylene melamine | TEM | Oral | Single dose of 2.5 to 5 mg. per day; 20 to 40 mg. for a course of one month | Occasional nausea |
| Triethylene phosphoramide | TEPA | Intramuscular | Daily dose is 0.2 mg. per kg. of body weight; 1.5 to 2.5 per kg. for a course | Local irritation |
| 1,4-Dimethanesulfonyl-oxybutane | GT 41; MYLERAN® | Oral | Daily dose is 2 to 6 mg.; 150 to 250 mg. for a course | None |

*General toxicity*—These agents produce depression of the bone marrow with leukopenia, thrombocytopenia and anemia. The clinical manifestations of bone marrow depression appear two to three weeks after a course of treatment; excessive doses result in severe bleeding, granulopenia and anemia.

*Special precautions*—These drugs are given with particular caution to patients with bone marrow disturbances, to patients recovering from a previous course of HN2, TEM or a related compound, and to patients with chronic lymphatic leukemia.

*Mechanism of action*—These drugs interfere with the proliferation of rapidly dividing normal and neoplastic cells, presumably because of their effect on nucleoprotein synthesis and chromosomal duplication. The cells of the blood-forming organs are particularly susceptible.

*Principles of treatment*—These drugs are given, under appropriate control, until a clinical response occurs, or until signs of toxicity appear. As the disease becomes resistant, more aggressive therapy is indicated in some cases, although the risk may be great. The orally effective compounds TEM and Myleran have also been used for maintenance therapy.

TABLE 5

URETHANE

Urethane (ethyl carbamate) is usually given orally, but it may be given intravenously or intramuscularly. Two to 4 gm. usually is administered daily in divided doses, and the total dose during a course of treatment may vary from 30 to 300 gm. Urethane may produce some degree of nausea and vomiting, and, less frequently, drowsiness.

*General toxicity*—When urethane is administered for a long time, it will produce bone marrow depression, with leukopenia, thrombocytopenia and anemia. Hepatic injury has been observed in a few instances.

*Mechanism of action*—It may act as an antimetabolite.

*Principles of treatment*—The drug is administered continuously and in adequate doses, if possible, until clinical improvement or bone marrow depression occurs. A maintenance dose may then be established in some of the cases.

TABLE 6

FOWLER'S SOLUTION

Solution of potassium arsenite (Fowler's solution) is given orally. When its administration is begun, 0.15 cc. (3 drops) usually is given three times a day. This dose is increased at the rate of 0.05 cc. (1 drop) per day until 1 cc. (20 drops) is being given three times a day or until evidence of toxicity or an adequate response occurs. The dose is then gradually decreased until a satisfactory maintenance dose is established.

*General toxicity*—Diarrhea, nausea and vomiting may occur when large doses are being administered. Skin eruptions and hyperkeratosis occur in some cases.

*Mechanism of action*—Potassium arsenite apparently exerts a general toxic effect on cell growth and division, and thus may interfere with the proliferation of leukemic cells.

*Principles of treatment*—In chronic myelogenous leukemia, after the disease has been brought under control, a maintenance dose is established.

TABLE 7

FOLIC ACID ANTAGONISTS

*(4-Amino Analogues of Folic Acid)*

| COMPOUND | COMMON NAME | ROUTE OF ADMINISTRATION | USUAL DOSE | ACUTE TOXICITY |
|---|---|---|---|---|
| 4-Aminopteroylglutamic acid | AMINOPTERIN®; 4-Amino PGA | Oral | 0.25, 0.5 or 1.0 mg. per day | None |
| 4-Amino-$N^{10}$-methyl pteroylglutamic acid | AMETHOPTERIN® METHOTREXATE® | Oral | 2.5 to 5.0 mg. per day | None |

*General toxicity*—These compounds produce a variety of toxic effects, including anorexia, oral ulceration, gastrointestinal disturbances including diarrhea, which may be bloody, and bone marrow depression with megaloblastosis. Recovery of the marrow usually occurs within 7 to 10 days after administration of the drug is stopped.

*Special precautions*—The smaller doses are used for children.

*Mechanism of action*—Folic acid is converted to a formyl derivative, folinic acid, which has many biologic functions, including the contribution of single carbon fragments to the synthesis of purine. The 4-amino folic acid analogues block the conversion of folic acid to folinic acid, thus interfering with synthetic processes in the cell, resulting in inhibition of cellular multiplication and tissue growth.

*Principles of treatment*—In acute leukemia, the folic acid antagonists are given at gradually increasing doses until evidence of toxicity appears, when administration of the drug is temporarily stopped, or until a hematologic remission occurs. An adequate trial of therapy may require three to four weeks or longer, and signs of toxicity may be induced several times before a therapeutic response occurs. When a remission occurs, the administration of the drug may be discontinued until relapse occurs, or it may be continued as maintenance therapy.

TABLE 8

6-MERCAPTOPURINE

6-Mercaptopurine (6-MP; PURINETHOL®) is administered orally. When treatment is begun, the daily dose is 2.5 mg. per kilogram of body weight. In an average course of treatment, the total dose ranges from 40 to 80 mg. per kilogram of body weight. In many instances, Purinethol may be continued at 2.5 mg. per kilogram of body weight (50 to 200 mg. in the usual case) daily for an indefinite period. Purinethol usually is well tolerated.

*General toxicity*—The drug may cause bone marrow depression associated with leukopenia, thrombocytopenia and anemia. Recovery usually occurs within 7 to 10 days after administration of the drug is stopped. Nausea associated with diarrhea may occur occasionally, and oral lesions have been observed.

*Mechanism of action*—6-MP presumably is a purine antagonist which interferes with nucleic acid synthesis, but this has not been proved in animals or man.

*Principles of treatment*—A daily dose of 2.5 mg. per kilogram of body weight usually is administered until a therapeutic response occurs. In some cases, a larger dose is necessary. If evidence of depression of the normal bone marrow elements appears, the dose should be decreased. In cases of leukemia, administration of a maintenance dose of 1.5 to 2.5 mg. per kilogram of body weight usually is continued during the period of hematologic response.

The proper application of these agents depends on the type of neoplastic process, the stage of the disease, and the particular experience of the physician. The use of each drug must also be determined in relation to the other available methods of treatment. Some indications for their use in the general management of far advanced cancer are presented in tables 9 to 21. It should be noted that nonspecific and supportive measures, such as blood transfusion and antibiotics, should be used as necessary.

TABLE 9

ACUTE LEUKEMIA

| AGE OF PATIENTS | CLINICAL STATUS | INITIAL THERAPY | SUBSEQUENT THERAPY | RESPONSE |
|---|---|---|---|---|
| Children | Acutely ill | ACTH; cortisone acetate or hydrocortisone acetate | As soon as the patient is improved on cortisone, antimetabolite therapy is started. If patient responds or becomes resistant to one agent, another type should be tried. Cortisone, Amethopterin and 6-MP produce remissions by different mechanisms and a patient resistant to one agent may respond to another | Clinical and hematologic response in 70% of cases; 50% of patients survive one year or more, and many obtain several remissions |
| | Fair condition<br>Leukocyte count high | 6-MP | | |
| | Leukocyte count low | 6-MP or Amethopterin | | |
| Young adults 15-30 | Acutely ill | ACTH; cortisone acetate or hydrocortisone acetate | 6-MP should be tried in all cases; Amethopterin is less effective | 25% obtain clinical and hematologic remissions for several months or longer |
| | Fair condition | 6-MP | | |
| Adults over 30 | | 6-MP, ACTH or cortisone acetate | 6-MP is basic therapy; ACTH and cortisone acetate are not very effective | 10 to 15% obtain clinical improvement for several months or longer |

*Comment*—Each drug should be given an adequate trial, which may require the production of some signs of toxicity. If the patient fails to respond to an adequate trial, or if a relapse occurs despite continued use of a drug, further improvement may be obtained, particularly in children, by the use of still another drug.

TABLE 10

CHRONIC MYELOGENOUS LEUKEMIA

| EARLY | INTERMEDIATE | FAR ADVANCED |
|---|---|---|
| X-rays (200 to 400 r) applied to the spleen | Larger doses of x-rays should be applied to the spleen | If platelet count is adequate: Larger doses of x-rays should be applied to the spleen. HN2 should be tried |
| Myleran, $P^{32}$, Fowler's solution, urethane and TEM all produce improvement | Disease may be controlled with Myleran, TEM and $P^{32}$ | If disease is in the acute phase and associated with thrombocytopenia: 6-MP should be tried, and cortisone acetate may reduce the bleeding tendency |
| No treatment | 6-MP should be administered to patients who do not respond adequately to x-ray therapy, Myleran, TEM, or $P^{32}$ | |

*Comment*—The duration of chronic myelogenous leukemia is not appreciably modified by therapy, and patients usually survive between three and four years after the diagnosis is made. Proper treatment will suppress the manifestations and keep the patient in relatively good condition during the major portion of the disease. As the disease progresses or the patient's response to one form of therapy lessens, it is desirable to try some other form.

TABLE 11

CHRONIC LYMPHATIC LEUKEMIA

| EARLY | INTERMEDIATE | FAR ADVANCED |
|---|---|---|
| Small doses of x-rays applied to the enlarged nodes | TEM should be administered carefully as long as the leukocyte count falls without any decrease in the hemoglobin or in the platelet count. Its administration should be discontinued if a bleeding tendency is imminent | Cortisone acetate may produce improvement by decreasing the bleeding tendency, by maintaining the concentration of hemoglobin and by reducing the size of enlarged nodes |
| Oral administration of TEM started very cautiously | $P^{32}$; same precautions as for TEM | X-ray therapy to the spleen and liver sometimes causes hematologic improvement |
| $P^{32}$ | Cortisone acetate, particularly if acquired hemolytic anemia is present | |
| No treatment | | |

*Comment*—Early, asymptomatic chronic lymphatic leukemia does not require any treatment. Treatment should be started cautiously, particularly with TEM, since the patient may be unusually sensitive to this agent. Cortisone acetate may produce improvement after the patient is no longer suitable for x-ray or TEM therapy.

## TABLE 12

### Hodgkin's Disease

| EARLY AND LOCALIZED | INTERMEDIATE AND GENERALIZED | FAR ADVANCED |
|---|---|---|
| Local excision | Local x-ray therapy | HN2 or TEM should be given an adequate trial. Dose should be determined by the hematologic status |
| Intensive, local x-ray therapy | If patient is ambulatory, TEM should be given to control the systemic symptoms. HN2 should be given to produce a more rapid response | Local x-ray therapy |
| Combination of HN2 and intensive, local x-ray therapy | | Cortisone acetate as a supportive measure |

## TABLE 13

### Lymphosarcoma

The varieties of lymphosarcoma present problems similar to those of Hodgkin's disease. X-ray therapy is the most important method of treatment. The less aggressive types of lymphosarcomas, such as the giant follicular lymphosarcomas, may respond to small doses of TEM or HN2, and cortisone acetate may cause marked tumor regression in some cases. The reticulum cell sarcomas, on the other hand, are often resistant to these agents, and only transient improvement may result from a course of HN2 or TEM. The biologic behavior of the disease must, therefore, be considered in selecting the method of treatment offering the best chance for a therapeutic response.

## TABLE 14

### Polycythemia Vera

$P^{32}$ is regarded as the agent of choice in the treatment of this condition, and treatment produces prolonged remissions. Spray x-ray therapy has a similar type of action. TEM produces hematologic and clinical improvement, but the remissions are usually shorter than those following $P^{32}$, and more frequent observation is necessary.

## TABLE 15

### Multiple Myeloma

X-ray therapy is useful for local painful lesions. Systemic therapy with $P^{32}$ and $I^{131}$ has produced symptomatic improvement. Urethane may be effective in inducing clinical and hematologic improvement in 15 to 20 per cent of the cases. In cases of acute or far advanced disease, cortisone acetate sometimes has given a rapid response, with improvement in the concentration of hemoglobin and relief of pain.

## TABLE 16

### Prostatic Cancer

Early cancer of the prostate is treated by radical prostatectomy or by transurethral resection to relieve local obstruction. In cases in which the disease is advanced, it is generally agreed that combined castration and estrogen therapy give the most satisfactory and prolonged response, although either method alone is also effective in 60 to 80 per cent of the cases. During a relapse, the dose of estrogen may be increased. X-ray therapy is used in treating local lesions not responding to hormonal control measures. These measures have been very effective in relieving discomfort and significantly prolonging life.

## TABLE 17

### Thyroid Cancer

Surgery and x-ray therapy are the major forms of treatment. Inoperable functional carcinoma of the thyroid may respond to radioactive iodine ($I^{131}$). This response may be enhanced by removing the normal thyroid gland and pretreating the patient with thiouracil, these measures increasing the avidity of the tumor for iodine. Generally, about 20 per cent of the patients with inoperable thyroid cancer show a substantial response to $I^{131}$.

TABLE 18

CANCER OF THE BREAST

| AGE OF PATIENTS | EARLY | INTERMEDIATE, INOPERABLE OR RECURRENT | FAR ADVANCED |
|---|---|---|---|
| Premenopausal to 5 to 10 years postmenopausal | Radical mastectomy with or without postoperative x-ray therapy | Surgical castration<br><br>Androgens may be given, but their administration should be stopped if patient is not responding to this treatment<br><br>Local x-ray therapy | Adrenalectomy in patients who have responded to previous castration<br><br>Cortisone acetate<br><br>HN2, TEM or TEPA in cases of generalized cancer<br><br>Intrapleural administration of $Au^{198}$ or HN2 in recurrent pleural effusions<br><br>Estrogens |
| 5 to 10 years or more post-menopausal | Radical mastectomy with or without postoperative x-ray therapy | Estrogens<br><br>Androgens<br><br>Application of x-rays to local lesions | Castration and adrenalectomy<br><br>Cortisone acetate<br><br>HN2, TEM or TEPA in cases of generalized cancer |

*Comment*—Breast cancer may run a variable, prolonged and remitting course. An orderly program of therapy should be followed, so that each agent used can be properly evaluated as to its clinical effect before administering another agent. By persistently applying these methods in proper situations, prolonged periods of palliation may be obtained in many cases. It is generally stated that 20 to 50 per cent of the patients obtain objective regression of the disease from hormonal control measures.

TABLE 19

CANCER OF THE LUNG

| EARLY AND LOCALIZED | INTERMEDIATE, INOPERABLE OR RECURRENT | FAR ADVANCED AND GENERALIZED |
|---|---|---|
| Surgical excision | X-ray therapy | Local application of x-rays to area causing discomfort |
| | HN2 should be used with x-ray therapy if the superior vena cava syndrome or recurrent pleural effusion is present. HN2 may be administered intrapleurally in cases of recurrent pleural effusion | HN2 may be tried in cases of symptomatic widespread disease |
| | $Au^{198}$ for recurrent pleural effusion | Oral administration of TEM |

*Comment*—The clinical improvement produced by HN2 is usually brief and lasts from three to eight weeks. Subsequent courses are less effective. From 40 to 60 per cent of the patients obtain some clinical benefit from treatment with HN2.

TABLE 20

OVARIAN CANCER

| EARLY AND LOCALIZED | INTERMEDIATE, INOPERABLE OR RECURRENT | FAR ADVANCED |
|---|---|---|
| Surgical excision | Application of x-rays to abdomen | Palliative operation |
| | Hormonal therapy has not been generally effective | Local x-ray therapy |
| | | Intraperitoneal injection of $Au^{198}$ for ascites |
| | | TEM |
| | | HN2 |

*Comment*—TEM has produced symptomatic improvement and objective regression of the disease in 30 to 40 per cent of cases of far advanced cancer. The favorable response usually lasts two to three months, but longer periods of improvement have been obtained.

TABLE 21

MISCELLANEOUS TUMORS

| EARLY | INTERMEDIATE, INOPERABLE OR RECURRENT | FAR ADVANCED |
|---|---|---|
| Operation or x-ray therapy | Local x-ray therapy | HN2 occasionally may produce a response and transient regression of the tumor in selected cases |
| | Palliative operation | Cortisone acetate as a supportive measure |
| | | Experimental chemotherapeutic agents should be tried in selected cases |

While this report is concerned with chemotherapeutic agents, their use is related to the alternate forms of treatment and the stage of the disease. By the judicious use of these drugs, considerable benefit can be obtained in many situations, and, furthermore, the recent interest in the chemotherapy of cancer has led to improvements in the over-all care of patients with inoperable neoplastic disease. Within the pattern of treatment for the various types of cancer suggested in this report, new therapeutic agents, after adequate clinical evaluation, can be introduced into their proper place.

(I wish to express my appreciation to the other members of the Chemotherapy and Medical Services of the Memorial Center for their work leading to the preparation of the tables included in this paper.)

# Psychologic Barriers to Rehabilitation of Cancer Patients

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THE psychologic impact of cancer and its therapy has only recently been subjected to formal investigation,[1-5] and the problems confronting the cancer survivor are just beginning to be understood. These problems usually consist of both realistic difficulties attendant on changed body form or function, and emotional or psychologic disturbances inherent in the resumption of patterns of living believed compromised by the disease and its treatment. The observations herein reported are based primarily on the responses of psychiatrically "normal" patients selected for study only because they had cancer in a particular site or because of the nature of the surgical procedure they had undergone.

Rehabilitation may be defined as the process by which the survivor of an experience damaging to body or mind is restored as closely as possible to his previous level of activities. It aims first at repair of physical damage and restoration of function of the damaged body part, or replacement by prosthesis, and then at the restoration of the total function of the individual. It must at times modify the environment by selective placement or by special implements. At times, rehabilitative efforts are defeated by the extent of body damage, or by the rigidity of the environment. It is not generally recognized that unsuccessful attempts at rehabilitation of the cancer survivor are more often due to his own psychologic and emotional problems than to physical and environmental factors.

There are very few studies on employment of cancer patients following surgery. Nevertheless, my impression based on clinical experience alone is that the vast majority of survivors are physically able to resume their usual occupations or activities. With certain exceptions, environmental demands or physical changes in body form and function by themselves do not interfere with resumption of work or other activities, and therefore physical rehabilitation other than conventional convalescence plays a relatively minor role.

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Impairment of productivity is usually related to psychologic factors.

To speak of "adjustment" to cancer or the results of therapy, such as a colostomy, is too indefinite, and to regard return to work as the chief criterion of rehabilitation is an oversimplification. There are many little "adjustments" to be made in every aspect of the patient's life. The way in which an individual has adjusted or continues to adjust can only be determined by a careful inventory of his activities. Therefore, he should be assessed in all significant activities in which his premorbid level of functioning can be compared with his present, especially his behavior in work, recreation and marriage. Levels of activity in these areas do not necessarily fluctuate together, and each can vary independently in the same individual.

One man returns to work at approximately his preoperative level but restricts social or sexual activities. Another is forced by circumstances to work full time, but he does so only at the cost of increased anxiety and the development of conversion phenomena and physiologic disturbances secondary to stress. Another is apparently at work full time, but soldiers on the job. Another shifts his employment to a job less demanding of the expenditure of energy. A housewife is back at housework, but foregoes "heavy cleaning," and lowers her standard of cleanliness. In none of these individuals is work restriction justified by their physical status. When work, either gainful employment for men and women, or housework for women, is restricted for other than physical reasons, two main sources can usually be identified: (1) hypochondriac notions of body injury and fragility, and (2) fears of unacceptability to others. One or both may be present in the individual.

The treatment of the cancer patient frequently consists of an extensive or "radical" operation. The surgical experience itself is often crucial to the development of ideas of crippling injury. Patients tend to equate the seriousness of the threat of the lesion with the extent of the operation—"bad diseases require big operations"—and to equate the extent of the operation with postoperative permanent deficits in health and performance.

Chances of survival may be seen as only "fifty-fifty," or a "toss-up," and the closeness to death or the gross mutilation is attested to by dreams of corpses, morgues, funerals, open graves, tombstones, angels of death, and attacks by dogs, gorillas and savages.

A lively preoperative expectation of serious body injury may be converted postoperatively into the belief that irremediable damage has taken place, and the hypochondriac response is established. This is most likely to happen in those who have had lifelong "masochistic problems," that is, those who have dealt with desires and wishes perceived as forbidden or dangerous, by self-inflicted punishments or unnecessary restriction of activity. Punishment is frequently seen in terms of physical injury. "I have lived just ahead of the executioner all my life, and I feel like I had lost a case, and had to go to the electric chair." When beliefs of irreparable body injury have been established, they are usually acted out by restriction of activity in all areas, but most obviously in restriction of work.

The notion of body injury is usually accompanied by a sense of fragility: "I treat myself like a soft-boiled egg, liable to break its shell at any moment." There is also a sense of loss of energy, or lessened "*élan vital*," which must carefully be husbanded to meet the inescapable demands of living. The sense of loss of energy and fragility is accompanied by the notion that the body has been rendered more vulnerable to other diseases, and, notably, to recurrence of cancer. This attitude is often reinforced by beliefs that previous hard work or energy expenditure has been responsible, as least in part,[6] for the development of cancer. Patients with such beliefs are reluctant to re-enter situations perceived as dangerous. Therefore, the hypochondriac response is frequently signaled by requests for part-time work, or work under special conditions that serve the purpose of shielding the individual from dangerous expenditure of energy.

The sense of body injury is supported by misconceptions of the physiologic role of the sacrificed organ in the intact body. A number of patients who have undergone a colostomy

state that the loss of the rectum must inevitably affect their digestive or absorptive powers, or that irrigation washes out nourishment as well as feces. Loss of the uterus and menstruation, with or without oophorectomy, may herald old age and depleted vitality. Loss of the pectoral muscles and axillary contents by radical mastectomy gives rise to beliefs of injury to the subjacent intrathoracic contents, notably the heart, after left mastectomy.

Any postoperative complications, such as phlebothrombosis or bronchopneumonia, may also strongly reinforce beliefs of body injury. Wound dehiscence after mastectomy rather regularly intensifies hypochondriac responses. Complications are sometimes ascribed to uncontrolled or recurrent cancer. Somatic responses to emotion, such as anorexia, insomnia, tachycardia and palpitation, commonly seen in depressions or anxiety states, and conversion phenomena may also be misinterpreted as evidence of debilitation or recurrent cancer.

Beliefs of unacceptability to others, predicated on self-rejection, limit work because most employment requires social interaction. Withdrawal from others realistically limits job opportunities. Relations with other workers and the employer may be strained by development of paranoid trends. Continuing at work may lead to anxiety and consequent psychosomatic symptoms.

Restriction in social contacts is frequently due to a sense of unacceptability to others who are not expected to accept the change in form, as after mastectomy, or the possibility of uncontrolled function, such as occurs after colostomy. Should any untoward event take place, massive rejection and condemnation are expected. For example, patients who have undergone a total gastrectomy fear that intestinal hypermotility may be audible or cause embarrassing symptoms. Or, frequently weight loss following total gastrectomy leads to social withdrawal because one is unacceptable if one looks sick.

The type of social activity foregone or limited may be explicit of the reason for restriction. For example, food-centered gatherings are often restricted for reasons of embarrassment by patients who have undergone a gastrectomy or colostomy, whereas vigorous activity is foregone by those with the hypochondriac response who resign themselves to leading "quiet lives."

Decreases in sexual activity may also be expressive of emotional disruptions. In men, when the hypochondriac reaction is responsible for restriction of sexual function, it appears shortly after surgery and occasionally in anticipation of it. It may follow operations on sites far removed from the genital tract, such as thoracotomy or laryngectomy, and the inhibition cannot conceivably be due to anatomic change. It may amount to total impotence, but, more frequently, it is manifested by decrease in frequency. The individual is usually quite frank in stating that he regards this activity as too taxing to his body, or that it was followed by undue fatigue and hence seemed debilitating.

Sexual restriction in women may be associated with fears of injury and with hypochondriasis in those women who have been frigid or who have merely tolerated intercourse. For other women habitually frigid, who do not exhibit the hypochondriac response, the operation and experience of illness seem justification enough for cessation of a disliked activity.

Sexual activity cannot be easily abstracted from the quality of marriage, determined long before illness.[7] In warm and supportive relationships, sexual relations tend to continue or else there is a mutual agreement on cessation for reasons of health, or otherwise. In ambivalent or hostile marriages, especially if there has been deterioration of economic status following illness, wives withhold marital privileges from invalided husbands. When they insistently demand sexual relations, husbands of female patients in such marriages are likely to reinforce the sense of injury.

Ambivalent or hostile family attitudes, particularly on the spouse's part, usually deter the patient in efforts to resume activity. The patient suffers a loss of self-esteem through statements or actions that militate against his or her recovery. The hypochondriac response on the part of the patient intensifies hostility from the spouse, and a vicious circle is set up.

Restriction of activities in all spheres can

result from depression, a common sequel to loss of an important organ. Psychomotor retardation and physical symptoms accompanying depression can be mistaken for signs of irremediable body injury, and reinforce the hypochondriac response. Unfortunately, the sense of weakness and fragility with restriction of activity and consequent deterioration in status and earning power, or loss of other valued activities, can itself cause depression.

Paranoid reactions, sometimes frankly delusional, are serious barriers to rehabilitation. They are commonly directed against the physician or other medical personnel, and are very resistant to treatment. They may or may not be associated with the hypochondriac response. They apparently occur in those people in whose developmental history body intactness or a special organ, such as the breast, has played an inordinately large part. This "high narcissistic investment" seems to have been maintained with considerable guilt, and the loss of the organ is unconsciously seen as punishment. In an effort to deal with intolerable feelings of guilt and self-directed rage, often suicidal in intensity, blame is projected outward on others. This mechanism is difficult to deal with, and usually blocks attempts at rehabilitation.

No attempt has been made in this communication to estimate the frequency of adverse responses to cancer and its treatment. More extensive studies are needed to clarify that issue. Moreover, although such reactions have been seen after many different types of operations, it is probably true that certain types produce more frequent or more serious reactions than others. Reactions of so great a degree as to produce serious management problems are, fortunately, uncommon. Nevertheless, a very large number of patients exhibit some adverse responses, usually mild and of relatively short duration.

Nothing has been said about treatment. Apparently prophylaxis is the best treatment. A warm relationship between the patient and the physician is essential. This relationship should permit the doctor to be seen as protective rather than threatening; it should permit easy communication and discussion of irrational beliefs and misconceptions, and it should allow a beneficial dependency, especially during the early stages. The resulting sense of trust is vital when the physician encourages attempts at restoration of activities.

### *Summary*

Patients who have undergone an operation for cancer may require extensive psychologic rehabilitation. Beliefs in irremediable body injury and unacceptability to others are frequently responsible for unnecessary restriction of activities. They are reinforced by postoperative complications, and psychosomatic symptoms secondary to anxiety or depression. The spouse may greatly help or hinder rehabilitation. A good patient-physician relationship, beginning with the initial diagnostic examination, is the patient's best guarantee against the development of crippling beliefs and their expression in unnecessary restriction of activities.

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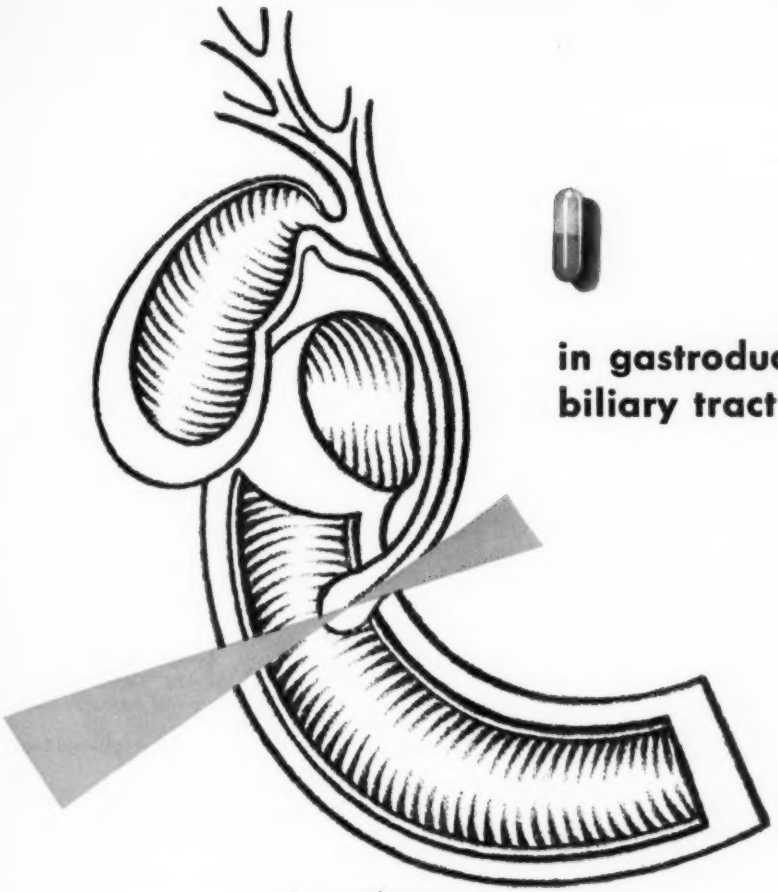



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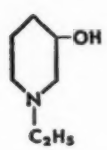


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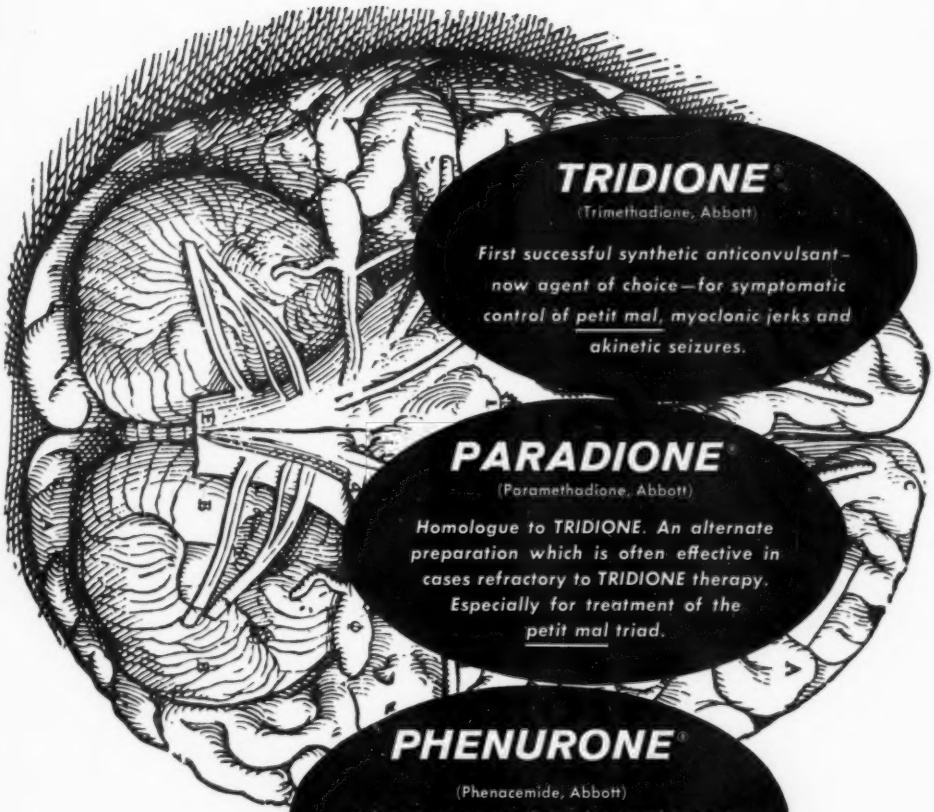

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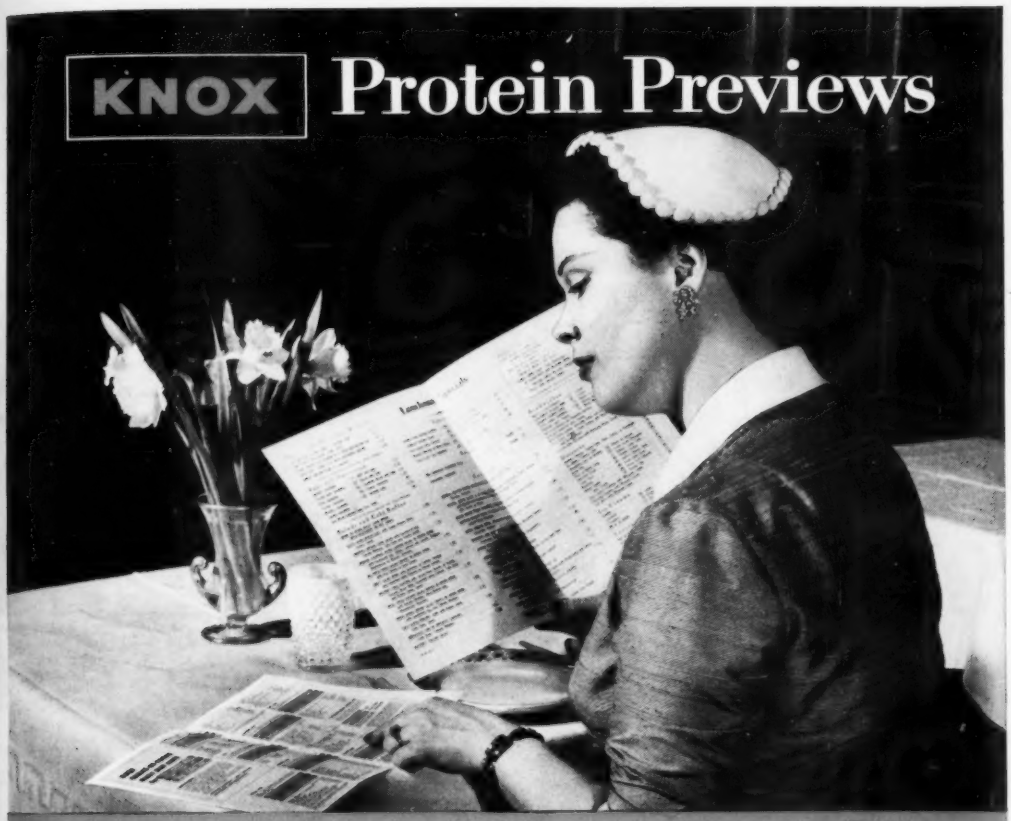

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*Please send me____copies of the new, color-coded "choice-of-foods diet list" chart.*

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# The High Price of Fat....

Here is where you have to clamp on a control.

One can paper the dining room wall with diet lists—but that will not help the patient understand the serious end-results of over-eating.

Where a chemical control is needed to offset the food craving which contributes to his obesity

**SANDRIX®**

—gives you that control—it depresses the appetite—gives the patient a feeling of well-being and energy which encourages activity and lessens dependence upon heavy food consumption.

**McNEIL**

*Supplied:* 5 mg. tablets, scored, green; imprinted 'McNeil'—bottles of 100 and 1,000. Samples on request. Also available in a pleasant-tasting elixir (colored amber); each 5 cc. (one teaspoonful) containing 5 mg.—pints and gallons.

**McNEIL LABORATORIES, INC. • PHILADELPHIA 32, PA.**

*Tourist Souvenir . . .*

Memorable beauty, pastoral charm, vacationer's diarrhea. . . .
To combat susceptible *infectious* forms, STREPTOMAGMA exerts potent antibacterial, adsorptive, and protective actions. Soothes the bowel, encourages normal stool development.
For common noninfectious diarrheas, prescribe KALPEC*—
pectin with kaolin in alumina gel.

**STREPTOMAGMA®** Wyeth

Dihydrostreptomycin Sulfate and Pectin with Kaolin in Alumina Gel

Philadelphia 2, Pa.

Lederle

# FOLBESYN*

Vitamins *Lederle*

A well-balanced, high-potency vitamin formula containing B-Complex and C

FOLBESYN provides B-Complex factors (including folic acid and $B_{12}$) and ascorbic acid in a well balanced formula. It does not contain excessive amounts of any one factor.

FOLBESYN Parenteral may be administered intramuscularly, or it may be added to various hospital intravenous solutions. It is useful for preoperative and postoperative treatment and during convalescence.

Dosage: 2 cc. daily. Each 2 cc. provides:

| | |
|---|---|
| Thiamine HCl ($B_1$) | 10 mg. |
| Sodium Pantothenate | 10 mg. |
| Niacinamide | 50 mg. |
| Riboflavin ($B_2$) | 10 mg. |
| Pyridoxine HCl ($B_6$) | 5 mg. |
| Ascorbic Acid (C) | 300 mg. |
| Vitamin $B_{12}$ | 15 micrograms |
| Folic Acid | 3 mg. |

FOLBESYN is also available in tablet form, ideal for supplementing the parenteral dose.

LEDERLE LABORATORIES DIVISION *AMERICAN Cyanamid COMPANY* Pearl River, New York

*REG. U.S. PAT. OFF.

sound sleep clear awakening

DORIDEN®

(glutethimide CIBA)

a totally new nonbarbiturate hypnotic and sedative

PRESENT CLINICAL EVIDENCE INDICATES DORIDEN IS NOT HABIT FORMING.

*Tablets (scored), 0.25 Gm. and 0.5 Gm.*

CIBA

SUMMIT, N. J.

# * New DRUGS AND INSTRUMENTS

*Information published in this department is supplied by the manufacturers of the products described.*

### • MICROSCOPE ILLUMINATORS

DESCRIPTION: Designed to simplify microscope operations, each of the three illuminators offers visual and photomicrographic applications with bright field, dark field and phase contrast illumination. The illuminators Models PG-26 and PR-27 are color corrected for precision photomicroscopy, and both are available with accessories. PL-25 is a general purpose illuminator that uses a 60-watt household lamp. Knob adjustment controls replace clamps and screws in all three models.
PRODUCER: Bausch & Lomb Optical Co., Rochester, N.Y.

### • SURGILOPE
**(New Package Form)**

PURPOSE: To package sutures.
DESCRIPTION: An outer metal foil envelope protects glassine envelope which contains 17 sterile strands of Anacap black braided silk sutures, each 18 in. long. Other sutures will be issued later in this new packaging.
PRODUCER: Davis & Geck, Inc., A Unit of American Cyanamid Company, Danbury, Conn.

### • COLOSTAT®

PURPOSE: Treatment of diarrhea.
COMPOSITION: Each fluid ounce contains:

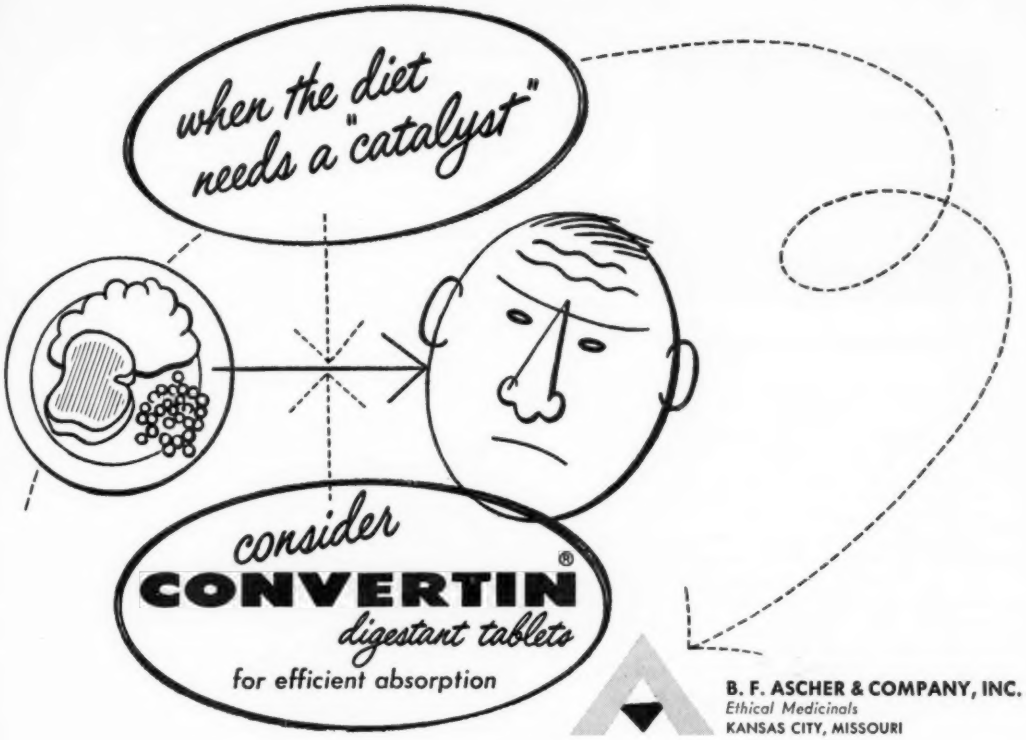
| | |
|---|---|
| Colloidal kaolin | 6.0 gm. |
| Calcium carbonate | 0.75 gm. |
| Sodium carboxymethylcellulose | 0.6 gm. |

DESCRIPTION: Provides demulcent, adsorbent and detoxicant action.
INDICATIONS FOR USE: Inflammatory bowel conditions, nonspecific gastroenteritis, gastrointestinal intoxications, colitis and other infections of the intestinal tract.
DOSAGE AND ADMINISTRATION: After each bowel movement, 1 to 2 tablespoonfuls until symptoms are controlled.
HOW SUPPLIED: Pint bottles.
PRODUCER: Schenley Laboratories, Inc., New York.

### • AUTOMATIC BLOOD PRESSURE RECORDER

DESCRIPTION: The electronic recorder, which measures both diastolic and systolic pressure, may be set at selected intervals from 30 seconds to one hour. It may be connected to a buzzer, bell or light system to summon the nurse when the blood pressure of a postoperative or cardiac patient reaches a preset level.
PRODUCER: The Colson Corporation, Elyria, Ohio.

*(Continued on page A-84)*




**B. F. ASCHER & COMPANY, INC.**
*Ethical Medicinals*
KANSAS CITY, MISSOURI

Your geriatric patient who doesn't respond to diet – or dyspeptic, underweight, or gallbladder patient – is he one of those unable to *utilize food?* If so, CONVERTIN, furnishing dietary catalysts necessary for absorption, may unlock for him, as it has for others, the nutritional benefit from diet.

Each CONVERTIN Tablet provides:

| | |
|---|---|
| *a sugar-coated outer layer of* | |
| Betaine Hydrochloride | 130.0 mg. |
| (Provides 5 minims Diluted Hydrochloric Acid U.S.P.) | |
| Oleoresin Ginger | 1/600 gr. |
| *surrounding an enteric-coated core of* | |
| Pancreatin (equiv. to 250 mg. U.S.P.) | 62.5 mg. |
| Desoxycholic Acid | 50.0 mg. |

The specially layered construction of CONVERTIN provides selective release of ingredients to assure efficient absorption in the stomach and small intestine.

Send in the coupon below for your bottle of 21 CONVERTIN Tablets. In the dosage of 1 or 2 tablets after meals, this provides a 3 to 7 days' supply, enough to demonstrate the tablet's value for the patient who needs its "catalytic" action. Growing numbers of prescriptions are now specifying CONVERTIN; clinical trial in your practice will prove to you, too, the effectiveness of this digestant.

**MAIL COUPON TODAY**

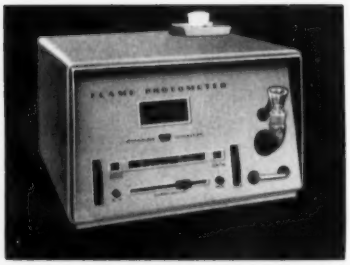
B. F. ASCHER & COMPANY, INC.
P. O. Box 5936— WESTPORT STATION— DEPT. E
KANSAS CITY, MO.

Please send me a trial sample of 21 CONVERTIN Tablets.

Dr. .....
(Please Print)

Address .....

City ..... Zone..... State.....




### • MODEL 146 FLAME PHOTOMETER

DESCRIPTION: The photometer may be operated either as a direct-reading instrument or as an internal-standard-ratio instrument, and each control is placed on a molded fiberglass panel for exact read-out of data. The photometer includes a burner that may be used on natural or manufactured gas, propane or acetylene; duo-prism monochromator which discriminates between elements; and an electronic amplifier, unaffected by vibration. An analysis may be accomplished in less than a minute with an accuracy of ± 1 per cent.
PRODUCER: The Perkin-Elmer Corp., Norwalk, Conn.

### • CORTICLORON NASAL SPRAY

COMPOSITION: Contains:
Cortisone acetate 0.5 per cent ..... 5 mg.
Chlor-trimeton gluconate 0.3 per cent (chlorprophenpyridamine gluconate) .. 3 mg.
INDICATIONS FOR USE: Relief of nasal symptoms associated with hay fever or other allergies. Average duration of effect is from two to six hours. Is safe for hypertensive, cardiac and ephedrine-sensitive patients.
DOSAGE AND ADMINISTRATION: Spray once or twice in each nostril every three or four hours.
HOW SUPPLIED: In 15 cc. plastic squeeze bottle.
PRODUCER: Schering Corporation, Bloomfield, N. J.

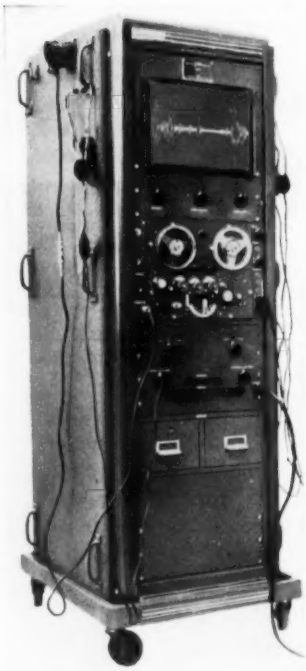
### • PYRIBENZAMINE® ANESTHETIC SOLUTION AND JELLY

PURPOSE: Topical anesthesia.
DESCRIPTION: Solution form is a 2 per cent clear, nonviscous, stable, sterile solution with 0.5 per cent chlorobutanol as a preservative.

Jelly form is a 2 per cent, stable, sterile, aqueous jelly, also with chlorobutanol.
INDICATIONS FOR USE: Urologic, proctologic, gastroscopic and otolaryngologic procedures and dental indications such as postextraction pain and temporary relief of painful caries.
HOW SUPPLIED: Solution in 30 ml. bottles. Jelly in 1 oz. tubes.
PRODUCER: Ciba Pharmaceutical Products, Inc., Summit, N. J.

### • VI-DAYLIN® DROPS (New Dosage Form)

PURPOSE: Nutritional supplement.
DESCRIPTION: A citrus-flavored mixture of seven vitamins for infants. Mixes in formula, milk, fruit juices and cereals.
DOSAGE AND ADMINISTRATION: For infants, 0.3 cc. to 0.6 cc. daily as directed by the physician.
HOW SUPPLIED: With calibrated dropper in 15 cc. and 30 cc. bottles.
PRODUCER: Abbott Laboratories, North Chicago.



### • EDUCATIONAL CARDIOSCOPE

PURPOSE: To teach electrocardiography and auscultation by audiovisual demonstration of electrocardiograms, heart sounds, vectorcardiograms, intracardiac blood pressure and other physiologic phenomena.
DESCRIPTION: The instrument incorporates two electrocardiographic amplifiers, a tape recorder with heart sound amplifier and suitable filters, and a 16 in. cathode ray tube having a long persistence screen on which the desired phenomenon is traced by an intense spot of light moving across the screen. Over-all dimensions are 68 by 22 by 18 in.
PRODUCER: Cambridge Instrument Co., Inc., New York.

*(Continued on page A-90)*

## Premenstrual Tension and Functional G-U Disorders

# *Bellergal*®

*Stabilizer of the entire Autonomic Nervous System*

| | |
|---|---|
| *Ergotamine tartrate* | *0.3 mg.* |
| *Bellafoline* | *0.1 mg.* |
| *Phenobarbital* | *20.0 mg.* |

*Adult Dosage: 4 to 6 tablets daily.*

SANDOZ

*Sandoz*
*PHARMACEUTICALS*
*HANOVER, N. J.*

# invitation to asthma?

## *not necessarily . . .*

Tedral, taken at the first sign of attack, often forestalls severe symptoms.

***relief in minutes*** . . . Tedral brings symptomatic relief in a matter of minutes. Breathing becomes easier as Tedral relaxes smooth muscle, reduces tissue edema, provides mild sedation.

***for 4 full hours*** . . . Tedral maintains more normal respiration for a sustained period—not just a momentary pause in the attack.

*Tedral provides:*

| | |
|---|---|
| Theophylline | 2 gr. |
| Ephedrine HCl | 3/8 gr. |
| Phenobarbital | 1/8 gr. |

*in boxes of 24, 120 and 1000 tablets*

# Tedral®

WARNER-CHILCOTT

*From Natural Vitamin C in Citrus*

# PREFERRED PROTECTION

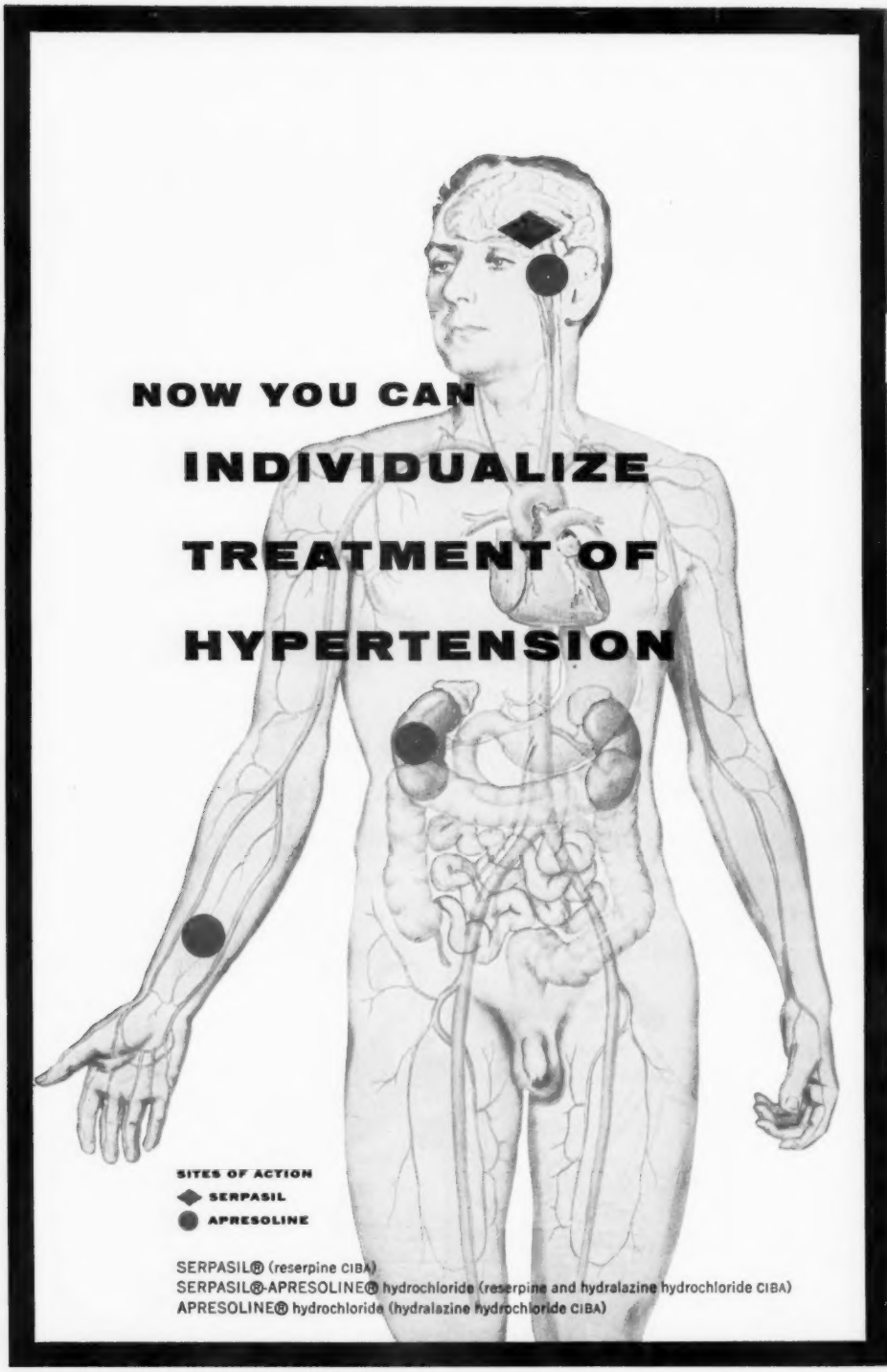
More and more physicians* find citrus preferable to synthetic ascorbic acid whenever supplementary vitamin C is indicated, since it promotes efficient and complete ascorbic acid utilization. For therapy (except in massive doses) or prophylaxis, citrus fruit or juice supplies vitamin C in a most readily utilized form . . . concomitantly providing vitamin A, important B complex factors (including inositol), essential minerals, amino acids, and protopectin.

**Chick, H.: Nutrition 7:59, 1953; Cotereau, H. et al.: Nature 161:557, 1948. Jolliffe, N. et al.: Clinical Nutrition; Hoeber, New York, 1950; pp. 586-601.*

**FLORIDA CITRUS COMMISSION**
*Lakeland, Florida*

FLORIDA *Citrus*

ORANGES • GRAPEFRUIT • TANGERINES


NOW YOU CAN
INDIVIDUALIZE
TREATMENT OF
HYPERTENSION
SITES OF ACTION
SERPASIL
APRESOLINE
SERPASIL® (reserpine CIBA)
SERPASIL®-APRESOLINE® hydrochloride (reserpine and hydralazine hydrochloride CIBA)
APRESOLINE® hydrochloride (hydralazine hydrochloride CIBA)

**For initial therapy—in all cases:**

SERPASIL, a pure crystalline alkaloid of rauwolfia root—particularly effective in the neurogenic forms of hypertension. *Acts centrally*—tranquilizes, moderately lowers blood pressure, slows heart rate.

# Serpasil®

**When combination therapy is indicated:**

SERPASIL-APRESOLINE, a combination product offering convenience and economy in the more complicated cases involving both neurogenic and humoral factors.

# Serpasil®-Apresoline®

**In more refractory cases requiring further individualization of dosage:**

APRESOLINE *acts centrally and peripherally* for a marked antihypertensive effect. Increases renal plasma flow—produces vasodilatation—inhibits pressor substances.

# Apresoline®

| | |
|---|---|
| **Serpasil** | Tablets, 0.1 mg., 0.25 mg. and 1.0 mg.<br>Parenteral Solution (for neuropsychiatric use only), 2.5 mg. per ml., in 2-ml. ampuls.<br>Elixir, 0.2 mg. per 4-ml. teaspoonful. |
| **Serpasil-Apresoline** | Tablets, each containing 0.1 mg. of Serpasil and 25 mg. of Apresoline.<br>Tablets, each containing 0.2 mg. of Serpasil and 50 mg. of Apresoline. |
| **Apresoline** | Tablets, 10 mg., 25 mg., 50 mg. and 100 mg.<br>Ampuls, 1 ml., 20 mg. per ml. |

CIBA
SUMMIT, N. J.

*Another Lederle "First"!*

# 1 MUMPS VACCINE

A practical immunizing antigen for prevention of mumps in children or adults where indicated.
Immunizes for about one year.
Packages: 2 cc. vial (1 immunization),
10 cc. vial (5 immunizations).

LEDERLE LABORATORIES DIVISION
*AMERICAN Cyanamid COMPANY*
PEARL RIVER, NEW YORK

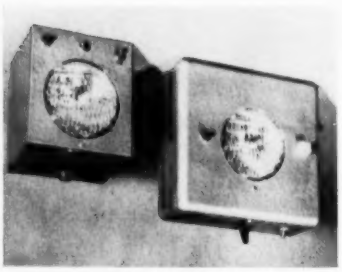
Lederle

**Vitamins at a truly therapeutic level for all stress conditions**

**Theron**
**(STUART)**

| Tablets: | Liquid: |
|---|---|
| 30's and 100's | 4 oz. bottles |
| Dose: | Dose: |
| 1 tablet daily | 1 teaspoonful daily |



**• SAFEGUARD LITE**

DESCRIPTION: Emergency battery-powered lights automatically turn on when electricity fails. "Lites" come equipped with battery test buttons and 6 volt G.E. sealed beam lamps. Cases are made of steel, are compact and lightweight. Available in five models, three having safety pilot lights. Four models are designed for use on walls, tables or floors, and several models are equipped with two lamps. Smallest model is portable.
PRODUCER: Jamil, Inc., Winter Park, Fla.

**• MONODRAL® BROMIDE WITH MEBARAL®**

PURPOSE: Anticholinergic agent for peptic ulcer and to reduce hyperactivity of the gastrointestinal tract.
COMPOSITION: Each tablet contains 5 mg. Monodral bromide and 32 mg. (½ gr.) Mebaral.
DOSAGE AND ADMINISTRATION: For the average peptic ulcer patient, 1 tablet three or four times daily. For other gastrointestinal disorders, 1 tablet three or four times daily until symptoms are controlled and then smaller doses to maintain relief.
HOW SUPPLIED: In bottles of 100.
PRODUCER: Winthrop-Stearns Inc., New York.

**• DIBULINE® SULFATE**

PURPOSE: Management of smooth muscle spasm.
DESCRIPTION: Dibuline sulfate, 25 mg. per cubic centimeter (Dibutoline sulfate, Merck), achieves full spasmolytic effect within 1 to 10 minutes after administration.
INDICATIONS FOR USE: Treatment of conditions requiring prolonged antispasmodic therapy, such as biliary spasm, urinary bladder spasm, spastic colon, functional pylorospasm, gastric and duodenal ulcer and acute gastroenteritis.
DOSAGE AND ADMINISTRATION: Subcutaneous or intramuscular dose for adults is 25 mg. (1 cc.), repeated if necessary after 20 to 30 minutes, and thereafter as indicated symptomatically.
HOW SUPPLIED: In 5 cc. rubber-capped vials.
PRODUCER: Sharp & Dohme, Division of Merck & Co., Inc., Philadelphia.

*(Continued on page A-92)*

**PATIENTS WITH A WEIGHT PROBLEM**

**WILL WELCOME YOUR SUGGESTION**

## *Only Half the Calories— but* ALL *the Protein, Minerals and B Vitamins of* MILK . . .

Recommend that overweight patients change to *new Instant* PET Nonfat Dry Milk—one of the most useful foods whenever a diet low in fat, moderately low in calories, but high in protein and calcium is indicated.

*Instant* PET Nonfat Dry Milk supplies equivalent amounts of all the essential protein, minerals and B vitamins of whole milk—only the fat is removed. Used as a beverage, its delicious *fresh milk flavor* is enjoyed by everyone who likes milk. Used in cooking, it enriches everyday foods with the most important nutritional values of milk.

And *Instant* PET Nonfat Dry Milk is easy-to-prepare, easy-to-store, easy-to-find in food stores everywhere—and its low-cost (less than half the price of ordinary milk) is attractive to people everywhere.

***Developed by Pet Milk Company makers of the original evaporated milk***

**PET MILK COMPANY • ARCADE BUILDING • ST. LOUIS 1, MISSOURI**

METICORTEN
PREDNISONE (metacortandracin)
more potent than cortisone or hydrocortisone • devoid of major undesirable side effects
METICORTEN,* brand of prednisone.
*T.M.
Schering
Scheting

**• CYSTOSCOPES WITH STANDARD CORD ADAPTATION**

DESCRIPTION: National Electric cystoscopes are now adapted for use with standard cystoscope light cords of any manufacture. This new design feature provides convenient interchangeability where use of more than one brand of cystoscope with one standard cord is desired.
PRODUCER: National Electric Instrument Co., Inc., Elmhurst, N.Y.

**• OXUCIDE**

PURPOSE: One-course therapeutic agent to treat pinworm and roundworm infestations.
COMPOSITION: Orange-flavored syrup of piperazine citrate containing the equivalent of 100 mg. piperazine hexahydrate per cubic centimeter or 500 mg. per teaspoonful.
DOSAGE AND ADMINISTRATION: Recommended course of treatment for pinworm is 10 days and five days for roundworm. Normal dosage is determined by body weight.
HOW SUPPLIED: In 16 oz. bottles containing 473 cc. per bottle.
PRODUCER: George A. Breon & Co., New York.

**• ACHROMYCIN® CRYSTALLINE OINTMENT WITH HYDROCORTISONE**

PURPOSE: Antibiotic.
DESCRIPTION: Available in two forms.

Achromycin ointment with hydrocortisone contains 30 mg. tetracycline hydrochloride and 20 mg. hydrocortisone per gram in a petrolatum-anhydrous lanolin base.

Achromycin ointment (ophthalmic) with hydrocortisone contains 10 mg. tetracycline hydrochloride and 15 mg. hydrocortisone per gram.
INDICATIONS FOR USE: Achromycin ointment for treatment of superficial skin infections, prevention of infections in wounds, abrasions and after surgery, and in certain types of dermatitis to reduce inflammation and promote healing.

Achromycin ointment (ophthalmic) for treat-

*(Continued on page A-94)*

# When you specify the Pfizer antibiotic of your choice *Stress Fortified* with the B-complex, C and K vitamins recommended by the National Research Council, be sure to write SF*

antibiotics *Stress Fortified* with vitamins include:

## ®Terramycin-SF

*Brand of oxytetracycline with vitamins*

CAPSULES 250 mg.

## ®Tetracyn-SF

*Brand of tetracycline with vitamins*

CAPSULES 250 mg.

ORAL SUSPENSION (fruit flavored) 125 mg./5 cc. teaspoonful

**The minimum daily dose of each antibiotic** *(1 Gm. of Terramycin or Tetracyn, or 600,000 units of penicillin)* **Stress Fortifies the patient** *with the stress vitamin formula* **recommended by the National Research Council:**

| | | | |
|---|---|---|---|
| Ascorbic acid, U.S.P. | 300 mg. | Calcium pantothenate | 20 mg. |
| Thiamine mononitrate | 10 mg. | Vitamin $B_{12}$ activity | 4 mcg. |
| Riboflavin | 10 mg. | Folic acid | 1.5 mg. |
| Niacinamide | 100 mg. | Menadione (vitamin K analog) | 2 mg. |
| Pyridoxine hydrochloride | 2 mg. | | |

**Trademark*

Pfizer

PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y.

ment of eye infections and noninfectious eye conditions such as keratitis, allergic conjunctivitis and chemical and heat burns.
HOW SUPPLIED: Achromycin ointment in 5 gm. tubes. Achromycin ointment (ophthalmic) in ⅛ oz. tubes with applicator tip.
PRODUCER: Lederle Laboratories Division, American Cyanamid Company, Pearl River, N.Y.

### • DONNA EXTENTABS®

PURPOSE: To provide spasmolysis without any sedation.
COMPOSITION: Each tablet contains:

| | |
|---|---|
| Hyoscyamine sulfate | 0.3111 mg. |
| Atropine sulfate | 0.0582 mg. |
| Hyoscine hydrobromide | 0.0195 mg. |

DESCRIPTION: Donna Extentabs provide uninterrupted spasmolytic effects of an intensity equivalent to one-third the active ingredients, uniformly maintained for 10 to 12 hours.
DOSAGE AND ADMINISTRATION: 1 tablet morning and night (at 12 hour intervals) for round-the-clock effects. If necessary, dosage may be adjusted upward with safety. Donna Extentabs are nontoxic in recommended dosage and can be administered safely over prolonged periods of time.
HOW SUPPLIED: Pink, coated tablets in bottles of 100 and 500.
PRODUCER: A. H. Robins Co., Inc., Richmond, Va.

### • CONVALETS® FILMTAB*

PURPOSE: To treat multiple vitamin deficiencies associated with physiologic stress.
DESCRIPTION: Therapeutic stress formula vitamins that provide five times the usual daily allowance of B complex vitamins and vitamin C.
HOW SUPPLIED: Bottles of 25, 100 and 500.
PRODUCER: Abbott Laboratories, North Chicago.
*Trademark

### • NUFACTON

PURPOSE: Treating nutritional deficiencies resulting from stressful situations.
COMPOSITION: Each tablet contains:

| | |
|---|---|
| BIFACTON® (vitamin $B_{12}$ with intrinsic factor concentrate) | ½ U.S.P. oral unit |
| Folic acid | 5 mg. |
| Thiamine hydrochloride | 5 mg. |
| Niacin amide | 75 mg. |
| Riboflavin | 5 mg. |
| Ascorbic acid | 100 mg. |
| Pyridoxine hydrochloride | 5 mg. |
| d-Panthenol (equivalent to 5 mg. calcium pantothenate) | 4.31 mg. |

*(Continued on page A-96)*


BASIC IN HYPERTENSION

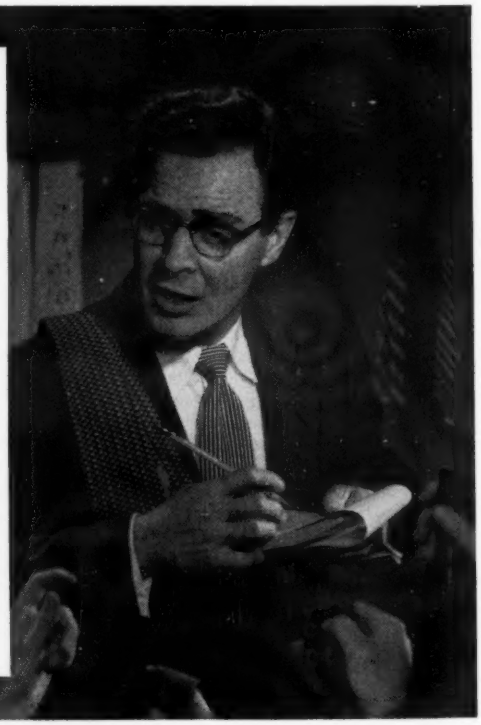
'Sandril'

(RESERPINE, LILLY)

In hypertension, 'Sandril' often produces the desired reduction of blood pressure. In severe cases, 'Sandril' supplements the action of 'Provell Maleate' (Protoveratrine A and B Maleates, Lilly).

SUPPLIED:
Tablets—0.1, 0.25, and 1 mg.
Elixir—0.25 mg. per 5-cc. teaspoonful.

Lilly



FOR EFFECTIVE
RELIEF OF
MUSCULOSKELETAL
SPASM
AND
ASSOCIATED PAIN

***hit both targets with one arrow***

# NEOCYTEN

TRADEMARK

***specific***
***effective***
***comprehensive***

Proved, potentiated salicylate therapy combined with physostigmine and homatropine . . . provides *simultaneous* relief of both pain and spasm with a high margin of safety even during extended use.

Each NEOCYTEN *Entab** (enteric-coated tablet) contains:

| | |
|---|---|
| Sodium Salicylate | 0.25 Gm. (4 gr.) |
| Para-Aminobenzoic Acid | 0.25 Gm. (4 gr.) |
| Ascorbic Acid | 20.0 mg. (⅓ gr.) |
| Physostigmine Salicylate | 0.25 mg. (1/250 gr.) |
| Homatropine Methylbromide | 0.50 mg. (1/120 gr.) |

**supplied:** bottles of 200, 500, and 1000 *Entabs.*

**dosage:** 2 *Entabs* four times daily, preferably before meals and at bedtime.

**THE CENTRAL PHARMACAL COMPANY**
*Products Born of Continuous Research*
SEYMOUR, INDIANA

*Trademark of The Central Pharmacal Company

INDICATIONS FOR USE: In conditions in which vitamin C and B deficiencies are known to occur, such as acute illness, convalescence, surgery, burns, infection, pregnancy and vitamin depletion states.
DOSAGE AND ADMINISTRATION: Recommended dosage as vitamin supplement is 1 or 2 tablets daily.
HOW SUPPLIED: In boxes of 24.
PRODUCER: Organon Inc., Orange, N. J.

### • ELPAGEN WITH CODEINE

PURPOSE: Treating conditions where high salicylate levels and effective analgesia are desired.
COMPOSITION: Each scored tablet contains:

| | |
|---|---|
| Codeine phosphate (May be habit-forming.) | ¼ gr. (16.2 mg.) |
| Sodium salicylate | 5 gr. (325 mg.) |
| Sodium para-aminobenzoate | 3 gr. (195 mg.) |
| Salicylamide | ½ gr. (32.5 mg.) |
| Ascorbic acid (vitamin C) as sodium ascorbate | 30 mg. |
| Dihydroxy aluminum aminoacetate | ½ gr. (32.5 mg.) |

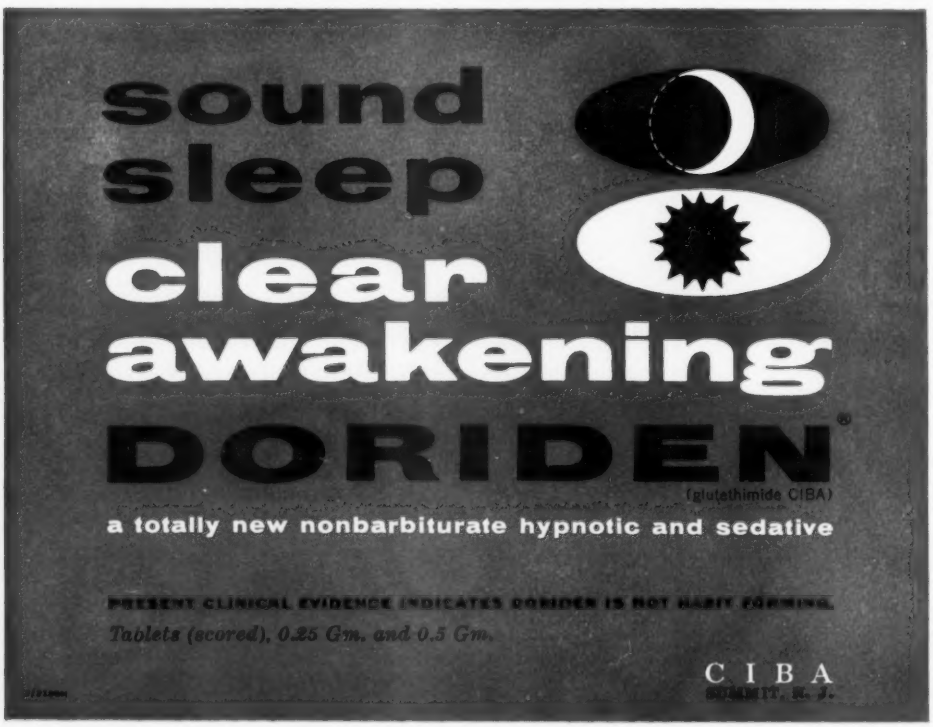
INDICATIONS FOR USE: Treating exacerbations of rheumatic fever, rheumatoid arthritis, neuralgia, gout, fibrositis, headache, muscular pains.
DOSAGE AND ADMINISTRATION: Usual dosage is 2 tablets three or four times daily.
HOW SUPPLIED: Bottles of 60.
PRODUCER: The E. L. Patch Company, Stoneham, Mass.

### • NEOBON CAPSULES

PURPOSE: An agent to retard the aging process.
COMPOSITION: Dark red, soft gelatin capsules containing lysine, methyl testosterone, ethinyl estradiol, liver-stomach substance, pancreatic substance, glutamic acid, rutin, ascorbic acid, folic acid, vitamins $B_1$, $B_2$, $B_6$, $B_{12}$, A, D and E, calcium pantothenate, niacin amide, iron and eight trace elements.
INDICATIONS FOR USE: Can be used as an adjuvant to specific therapy, and to combat decreased gonadal function, prevent iron deficiency and nutritional anemias, provide pepsin and pancreatic enzyme activity, and to meet the special nutritional needs of older persons.
DOSAGE AND ADMINISTRATION: 1 capsule three times daily with meals.
HOW SUPPLIED: Bottles of 60.
PRODUCER: J. B. Roerig & Co., Chicago.

### • CORRECTION

On page A-72 of the April 1955 issue, the name of the Hoffmann-La Roche, Inc. product 'NOLUDAR ROCHE' was spelled incorrectly.

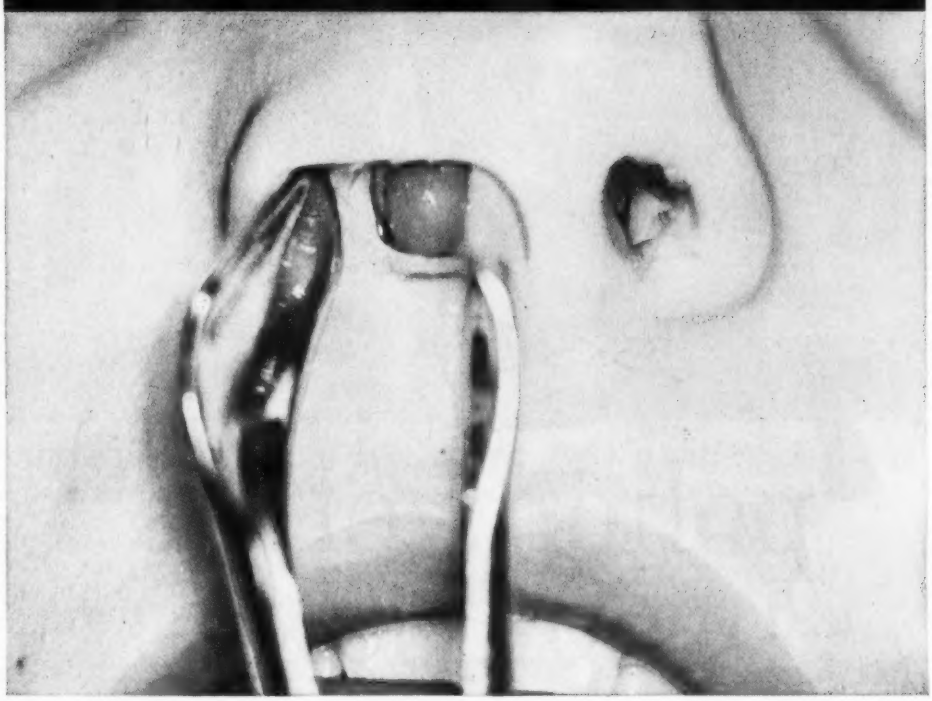


# HydroCortone®

(HYDROCORTISONE, MERCK)

## *Patients with hay fever show decided improvement within 24 hours*

**MAJOR ADVANTAGES:** Greater anti-allergic action than cortisone; smaller doses produce equivalent therapeutic response.



HYDROCORTONE is one of the most effective agents available for combating the distressing symptoms accompanying hay fever and vasomotor rhinitis.[1] However, systemic hormonal therapy should be reserved for those cases which fail to respond to less potent medication, or which are accompanied by asthma. In suitable candidates, steroid therapy produces prompt relief in a high percentage of patients. Tapering off of dosage is desirable since this may prolong the duration of remission after therapy is discontinued.

**SUPPLIED: ORAL**—HYDROCORTONE Tablets: 20 mg., bottles of 25, 100, and 500 tablets; 10 mg., bottles of 50, 100, and 500 tablets; 5 mg., bottles of 50 tablets.

SHARP & DOHME

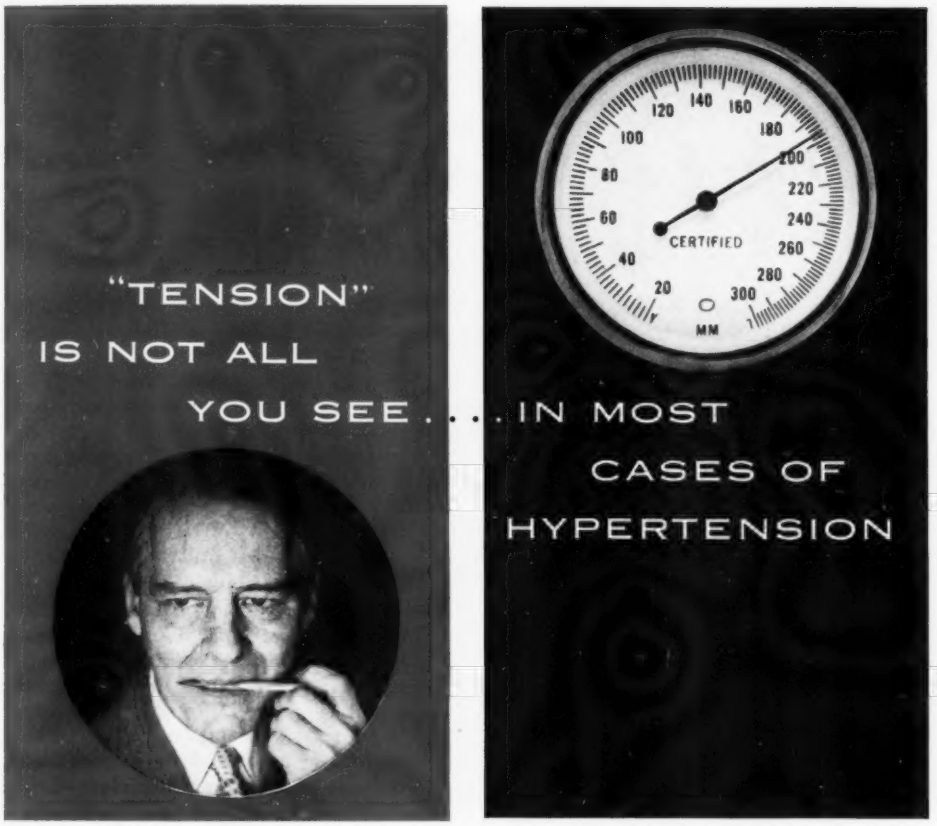
Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

1. LUKENS, F. D. W., *The Medical Uses of Cortisone*, The Blakiston Company, Inc., New York, pp. 331, 341, 1954.

poliomyelitis
prophylaxis
pitman·moore
company

*division of Allied Laboratories, Inc.*
*Indianapolis 6, Indiana*

*an original producer of poliomyelitis vaccine (Salk)*
*in one of America's largest biological laboratories*




*keep the blood pressure down longer and the patient calm with*

# Veralba/R*

PROTOVERATRINES A AND B WITH RESERPINE

In mild, moderate, and severe hypertension, VERALBA/R usually maintains blood pressure at approximately normal levels indefinitely. It offers "combined" drug therapy that is both safe *and* effective. Establishing precise dosage is a simple process with VERALBA/R, and side effects are usually insignificant.

*Supplied* in bottles of 100 and 1,000 scored tablets, each containing 0.4 mg. of protoveratrines and 0.08 mg. of reserpine.

*TRADEMARK

*Standardized with mathematical accuracy . . . by chemical assay*

**PITMAN • MOORE COMPANY**
DIVISION OF ALLIED LABORATORIES, INC. INDIANAPOLIS, INDIANA

# Meat...

## *Dietary Cholesterol and Vascular Sclerosis*

Recent studies reaffirm the "hypothesis that atherosclerosis is fundamentally a metabolic disease subject to important dietary influences"[1] and do much to refute contentions that foods containing cholesterol should be avoided in general diets.

Arterial disease resembling that in human subjects was produced in Cebus monkeys fed diets high in cholesterol and low in sulfur amino acids. Within 2 to 8 weeks after initiation of the regimen serum concentration of cholesterol rose to levels of 300 to 800 mg. per 100 ml. "The hypercholesterolemia could be largely prevented by feeding 1 gram per day of dl-methionine or l-cystine as supplements to the diet." Also, the elevated cholesterol levels "could be restored to normal by feeding 1 gram of dl-methionine but only partially restored by 0.5 gram of l-cystine daily."

According to the investigators, the "vascular lesions were in the ascending aorta but extended from the valves of the left ventricle to the proximal portions of the carotid and femoral arteries . . . The aortic lesions were chiefly characterized by the presence of lipid-laden phagocytes and increase in collagen and elastic fibers. The lipids were in part cholesterol derivatives."

Cholesterol, an essential metabolite produced in intermediary metabolism,[2] is biosynthesized from dietary protein, fat, and carbohydrate.[3] Normally, its synthesis is exquisitely controlled to insure adequacy as well as to protect against an oversupply.[4] Furthermore, considerable evidence indicates that an increased cholesterol intake is not an etiologic factor in alleged aberrations of cholesterol metabolism such as atherosclerosis.

In widely variable amounts, cholesterol occurs in foods of animal origin—meat, poultry, fish and marine foods, eggs, milk products—all foods of great nutritive value.[3] Present knowledge in no way warrants alteration in the customary consumption of these foods because of their contained cholesterol.

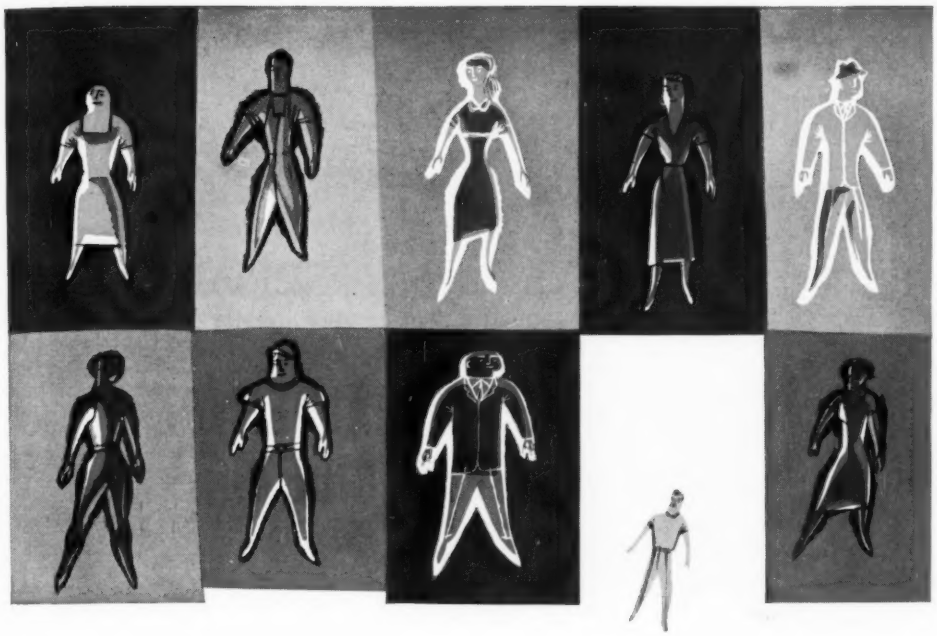
Skeletal muscle of beef, lamb, pork, and veal provides but small amounts of cholesterol, approximately 0.06 Gm. per 100 Gm. moist weight of meat.[5] Since atherosclerosis may interfere sharply with normal nutrition, the patient should consume diets rich in protein foods (such as meat), vitamins, and fruit.[6] In addition to high quality protein, meat supplies valuable amounts of needed B vitamins and essential minerals.


1. Mann, G. V.; Andrus, S. B.; McNally, A., and Stare, F. J.: Experimental Atherosclerosis in Cebus Monkeys, J. Exper. Med. *98*:195, 1953.
2. Okey, R.: Use of Food Cholesterol in the Animal Body; Relation of Other Dietary Constituents, J. Am. Dietet. A. *30*:231 (Mar.) 1954.
3. McLester, J. S., and Darby, W. J.: Nutrition and Diet in Health and Disease, ed. 6, Philadelphia, W. B. Saunders Company, 1952, pp. 517-518.
4. Editorial: The Biosynthesis of Cholesterol, J.A.M.A. *152*:1435 (Aug. 8) 1953.
5. Okey, R.: Cholesterol Content of Food, J. Am. Dietet. A. *21*:341 (June) 1945.
6. Wright, I. S.: Arteriosclerosis, in Stieglitz, E. J.: Geriatric Medicine, Medical Care of Later Maturity, ed. 3, Philadelphia, J. B. Lippincott Company, 1954, chap. 28, p. 413.


The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

**American Meat Institute**

**Main Office, Chicago... Members Throughout the United States**



**9 OUT OF 10 ANEMIC PATIENTS CAN BE TREATED WITH**

# PERIHEMIN*

Hematinic

Each PERIHEMIN Capsule contains every known hemopoietic factor:
Vitamin $B_{12}$ with Intrinsic Factor Concentrate...⅓ U.S.P. Oral Unit;
Vitamin $B_{12}$ (additional)...5 mcgm.; Ferrous Sulfate (Exsiccated)...192 mg.;
Folic Acid...0.85 mg.; Ascorbic Acid (C)...50 mg.;
Insoluble Liver Fraction...50 mg.

Two forms: Capsules and JR Capsules for children. JR Capsules
are approximately one-quarter the potency of this formula.
Either form in bottles of 100 and 1,000.

Lederle LEDERLE LABORATORIES DIVISION *AMERICAN Cyanamid COMPANY* PEARL RIVER, NEW YORK

*REG. U.S. PAT. OFF.

# It Has What it Takes For CHEMICAL DISINFECTION OF SHARP SURGICAL INSTRUMENTS

You can rely on

## B-P FORMALDEHYDE GERMICIDE to...

contains HEXACHLOROPHENE (G-11*)

**KILL** vegetative pathogens and spore formers within 5 minutes.*

**KILL** the spores themselves within 3 hours.*

**KILL** tubercle bacilli within 5 minutes.*

*Trademark of Sindar Corp.

**SUGGESTION! B-P CONTAINERS** are all especially designed for convenience in conjunction with the use of B-P GERMICIDE.

Used as directed, it will not injure keen cutting edges, points of hypodermic and suture needles, scissors and other 'sharps' . . . nor rust, corrode or otherwise damage metallic instruments.

IT'S THE ECONOMICAL ANSWER towards keeping annual costs for solutions and instrument replacement and repairs at a minimum. May be used repeatedly if kept undiluted and free of foreign matter.

*Comparative chart sent on request

*Ask your dealer*

**PARKER, WHITE & HEYL, INC.**
**Danbury, Connecticut, U.S.A.**

# for otitis

# 'AEROSPORIN'® SULFATE

POLYMYXIN B SULFATE WITH PROPYLENE GLYCOL

# OTIC SOLUTION STERILE

*Specifically aimed at aural pathogens—*

**bactericidal** to most gram-positive and gram-negative organisms, particularly *Ps. aeruginosa*, the commonest cause of otitis externa.

**fungicidal** to most of the dermatomyces found in the ear.

**For otitis externa,** whether acute or chronic, an exceptionally high percentage of complete clearance in a short time.

**For chronic otitis media** (when the ear drum is perforated); preferably in conjunction with systemic therapy.

Bottles of 10 cc. (with dropper)

**Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe 7, New York**

*To counteract extremes of emotion*

# Desbutal®

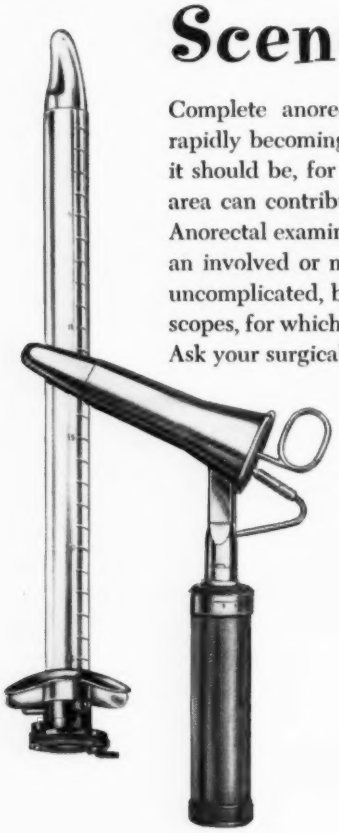
**(DESOXYN® *plus* NEMBUTAL®)**

DESBUTAL gives the disturbed patient a new sense of well-being and energy, while calming his tensions and anxieties. One capsule of this stimulant-relaxant represents 5 mg. DESOXYN Hydrochloride (Methamphetamine Hydrochloride, Abbott), and 30 mg. NEMBUTAL Sodium (Pentobarbital Sodium, Abbott). Bottles of 100 and 1,000. Abbott

506130

# Scene in your office?

Complete anorectal examination – digital, anoscopic, sigmoidoscopic – is rapidly becoming a part of every complete physical examination. This is as it should be, for every diagnosis of cancer and precancerous lesions in this area can contribute greatly to raising the present low percentage of cures. Anorectal examination, as many thousands of doctors have discovered, is not an involved or mysterious procedure. It is made even easier by the use of uncomplicated, brilliantly illuminated Welch Allyn anoscopes and sigmoidoscopes, for which your regular WA battery handle serves as the power source. Ask your surgical supply dealer to show you these practical instruments.



Copies of the helpful Welch Allyn booklets "Anal and Lower Rectal Lesions" and "Proctologic Examination" are available without charge from your WA dealer or from Welch Allyn, Inc., Skaneateles Falls, N. Y.

**WELCH ALLYN**

## Easy-to-use Rectal Instruments

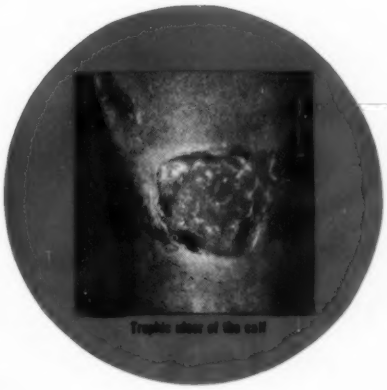
# TREAT this difficult condition with

# Parenzyme®

NATIONAL

*Intramuscular* trypsin

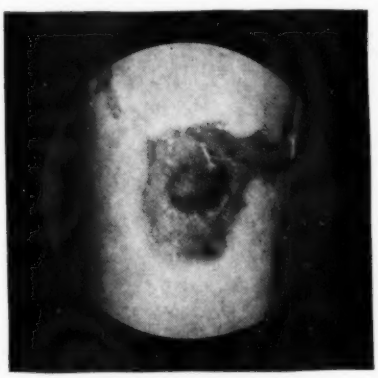
- Safe
- Not an anticoagulant
- Compatible with antibiotics and other indicated therapy



Trypsin dose of the calf

**BEFORE:**

Patient, an elderly housewife, had congestive heart failure and 4-plus edema in the infected leg. This highly inflamed lesion continued to spread despite antibiotics and topical enzyme preparations.



**AFTER:**

**Parenzyme Intramuscular Trypsin was given intragluteally, 0.5 cc. t.i.d. Within one week edema and redness subsided.**

Note: Additional information sent on request.

TIME BETWEEN PHOTOS: 8 WEEKS.

# OBTAIN

## striking improvement

**Other Indications:**

Skin ulcers
decubitus
diabetic
varicose

Traumatic wounds
slow-healing wounds
bruises
contusions
black eyes

Vascular disorders
phlebitis
thrombophlebitis
phlebothrombosis

Ophthalmic disorders
iritis
iridocyclitis
chorioretinitis

**Important Clinical Reports:**

Innerfield, I., *Trypsin Given Intramuscularly in Chronic, Recurrent Thrombophlebitis, J.A.M.A.*, 156:-1056-1058 (Nov. 13) 1954. Golden, H., *Intramuscular Trypsin, Its Effect in 83 Patients with Acute Inflammatory Disorders, Del. State Med. J.*, 26:267-270 (Oct.) 1954.

**DOSAGE:** 2.5 mg. (0.5 cc.) intragluteally q. 6 h. until improvement results; q. 12 h. thereafter.

**SUPPLIED:** 5-cc. multiple-dose vials (5 mg. trypsin/cc.).

**The National Drug Company,** Philadelphia 44, Pa.

- highly soluble in both acid and alkaline body fluids, especially at pH of renal tubules
- high plasma levels rapidly attained
- no alkalinization or forcing of fluids required
- single sulfonamide - not a mixture
- no danger of secondary fungus infections
- wide antibacterial range

you prescribe
these distinctive features
when you prescribe . . .

Hoffmann - La Roche Inc • Roche Park • Nutley 10 • N.J.

GANTRISIN® –brand of sulfisoxazole (3,4-dimethyl-5-sulfanilamido-isoxazole)

**Upjohn**

# Ulcer protection that lasts all night:

# Pamine*-Phenobarbital Elixir

BROMIDE

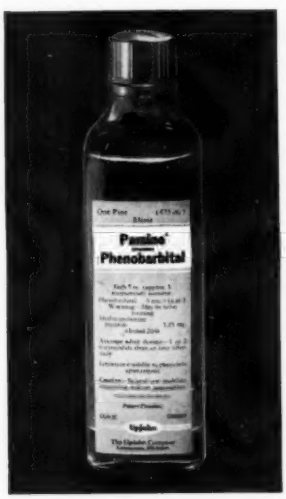
*Each 5 cc. (approx. 1 tsp.) contains:*

| | |
|---|---|
| Phenobarbital | 8.0 mg. (⅛ gr.) |
| Methscopolamine bromide | 1.25 mg. |
| Alcohol | 20% |

*Dosage:*

1 to 2 teaspoonfuls three or four times daily, depending upon requirements in the individual patient.

*Supplied:* Pint bottles.




*REGISTERED TRADEMARK FOR THE UPJOHN BRAND OF METHSCOPOLAMINE

The Upjohn Company, Kalamazoo, Michigan

*the soothing, protective, healing*[1-4] *influence of*

# DESITIN® OINTMENT

*is persistent*

because it adheres longer to the skin areas being treated . . . does not liquefy or crumble at body temperature, nor is it decomposed by secretions, perspiration, exudate, urine, or excrement.

Non-sensitizing, non-irritant Desitin Ointment... rich in cod liver oil... has proven clinically dependable for over a quarter century in... **diaper rash • eczemas intertrigo • wounds** (especially slow healing) **external ulcers • perianal dermatitis**

Tubes of 1 oz., 2 oz., 4 oz., and 1 lb. jars.

**samples** and reprints available from

**DESITIN** CHEMICAL COMPANY • 70 SHIP STREET PROVIDENCE 2, R. I.

1. Grayzel, H. G., Heimer, C. B., and Grayzel, R. W.: New York St. J. M. 53:2233, 1953.
2. Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediatrics 68:382, 1951.
3. Behrman, H. T., Combes, F. C., Bobroff, A., and Leviticus, R.: Ind. Med. & Surg. 18:512, 1949.
4. Turell, R.: New York St. J. M. 50:2282, 1950.

*Modern*
*Unique*
*Exclusive*

# new

# Cortril® Vaginal tablets

brand of **hydrocortisone**

Using CORTRIL Vaginal Tablets as supportive therapy in conjunction with usual measures, 18 investigators* treated monilial, trichomonal, senile, allergic, and nonspecific vaginitis. They obtained a good to excellent response in 90 per cent of patients.

CORTRIL, by virtue of its anti-inflammatory action, reduces local edema and inflammation in vaginitis. The resultant relief from vulvovaginal itching and discharge is often obtained within minutes or hours, as contrasted with two to three days with ordinary measures.

**administration:** Insertion of 1 or 2 tablets daily. **supplied:** 10 mg. tablets.

**Personal communications*

PFIZER LABORATORIES *Division, Chas Pfizer & Co., Inc.* Pfizer *Brooklyn 6, New York*

## a stabilizing agent for the mentally or emotionally disturbed

Unlike the barbiturates, RAU-SED is not a hypnotic when given in proper dosage and will not diminish the patient's alertness. It may be effectively employed as a tranquilizer to relieve tension or anxiety in a wide variety of conditions.

# RAU-SED

SQUIBB RESERPINE

0.1 and 0.25 mg. tablets, bottles of 100 and 1000

0.5 mg. tablets, bottles of 50 and 500

1.0 mg. tablets, bottles of 30, 100 and 500

2 ml. ampuls for parenteral administration, each ml. containing 2.5 mg. "RAU-SED" IS A SQUIBB TRADE-MARK

SQUIBB

*FOR SUPERIOR PERFORMANCE—*

*in Antibiotic Therapy—* **POLYCYCLINE**
*a tetracycline produced by a unique process of direct fermentation*

**BRISTOL LABORATORIES INC.**
**SYRACUSE, NEW YORK**

# *FOR SUPERIOR PERFORMANCE* IN ANTIBIOTIC THERAPY

***—effective, safer, more sustained action with this newest broad-spectrum antibiotic***

Polycycline—available in many dosage forms—affords significant clinical advantages in broad-spectrum antibiotic therapy:

**Effective in broad range**

—against Gram-positive and Gram-negative organisms, certain rickettsiae and large viruses.

**Greater tolerance**

—markedly lower incidence and severity of adverse side effects.

**Greater solubility**

—than chlortetracycline, yielding quicker absorption and increased diffusion in body fluids and tissues.

**Greater stability**

—in solution than chlortetracycline or oxytetracycline, assuring higher, more sustained blood levels.

•

Polycycline is a tetracycline produced by the unique Bristol process of direct fermentation. Its basic structural formula is free of a chlorine atom (present in chlortetracycline), and of an hydroxyl group (present in oxytetracycline).

*Your pharmacist has all dosage forms of Polycycline available for your prescription:*

**POLYCYCLINE SUSPENSION WITH TRIPLE SULFONAMIDES**

Coconut oil suspension of tetracycline with three sulfonamides. In concentration of 125 mg. tetracycline HCl with 167 mg. each of sulfadiazine, sulfamerazine and sulfamethazine per 5 cc.; in bottles of 2 fl. oz.

**POLYCYCLINE AQUEOUS '250' or AQUEOUS '125'**

An aqueous suspension ready to use without reconstitution. Stable for 18 months without refrigeration. Highly palatable, cherry flavor. As calcium tetracycline equivalent to 250 mg. (or 125 mg.) tetracycline HCl per 5 cc.; in bottles of 1 fl. oz.

**POLYCYCLINE SUSPENSION '250'**

A really palatable oil suspension, requiring no dilution or reconstitution. Needs no refrigeration—stable for 18 months. In concentration of 250 mg. tetracycline HCl per 5 cc.; in bottles of 1 fl. oz.

For accurate dosage in small amounts. In concentration of 100 mg. tetracycline HCl per cc.; in bottles of 10 cc. with dropper calibrated for administration of 25 mg. or 50 mg.

**POLYCYCLINE PEDIATRIC DROPS**

For deep intramuscular injection. In single-dose vials of 100 mg. tetracycline HCl per vial.

**POLYCYCLINE INTRAMUSCULAR**

Handy form for oral use, in two potencies of tetracycline HCl. In capsules of 100 mg.; in bottles of 25 and 100. In capsules of 250 mg.; in bottles of 16 and 100.

**POLYCYCLINE CAPSULES**

**POLYCYCLINE AQUEOUS PEDIATRIC DROPS**

As calcium tetracycline equivalent to 100 mg. tetracycline HCl per cc.; in bottles of 10 cc. with dropper calibrated at 25 mg. and 50 mg.

**POLYCYCLINE OINTMENT WITH 2% XYLOCAINE***

—30 mg. tetracycline HCl with 20 mg. Lidocaine (as the base), per gram.

**POLYCYCLINE OPHTHALMIC OINTMENT WITH 2% XYLOCAINE***

—10 mg. tetracycline HCl with 20 mg. Lidocaine (as the base), per gram.

*®OF ASTRA PHARM. PROD. INC. FOR LIDOCAINE.

***When you think of Tetracycline, think of***

**Bristol**
LABORATORIES INC.
SYRACUSE, NEW YORK

# POLYCYCLINE®

(Tetracycline HCl Bristol)

*in times of "STRAIN and STRESS"*

# STRESSCAPS*

Stress Formula Vitamins Lederle

When the body is subjected to unusual physiologic stress, the need for dietary supplementation with the essential vitamins is at its greatest. Such need arises:

After sustaining fractures and other serious trauma.
When there has been serious vitamin depletion.
After sustaining second or third degree burns.
In severe illness. In postoperative states.

| Each Capsule Contains: | | | |
|---|---|---|---|
| Thiamine Mononitrate ($B_1$) | 10 mg. | Pyridoxine HCl ($B_6$) | 2 mg. |
| Riboflavin ($B_2$) | 10 mg. | Vitamin $B_{12}$ | 4 megm. |
| Niacinamide | 100 mg. | Folic Acid | 1.5 mg. |
| Ascorbic Acid (C) | 300 mg. | Calcium Pantothenate | 20 mg. |
| | | Vitamin K (Menadione) | 2 mg. |

LEDERLE LABORATORIES DIVISION *AMERICAN Cyanamid COMPANY*
PEARL RIVER, NEW YORK

Lederle

*REG. U. S. PAT. OFF.

# THE MEDICAL *Bookman*

## ► UROLOGY

*Edited by Meredith Campbell, M.D., Emeritus Professor of Urology, New York University, New York. With 51 contributors. Vol. 1, 2 and 3. 2,356 pages with 1,148 figures. 1954, W. B. Saunders Company, Philadelphia and London. $60.00.*

Opening with a discussion of the anatomy, surgical anatomy, and physiology of the genitourinary tract, this comprehensive work continues with a section devoted to the principles of diagnosis. Unfortunately only translumbar aortography is presented, with no mention of percutaneous retrograde aortography.

An interesting discussion of the pathology of obstruction of the urinary tract is followed by an informative presentation of the anomalies of the urinary tract, their symptoms, diagnosis and treatment. Despite the author's statement to the contrary, there is some evidence that the 17-ketosteroids are useful in determining the sex of pseudohermaphrodites.

The next section deals with infections and inflammations of the urinary tract, including tuberculosis, a brief but thorough review of the use of antibiotics, sulfonamides, urinary antiseptics and arsenicals, and a discussion of urinary tuberculosis.

Succeeding sections cover venereal diseases and other infections of the male genital tract; problems of infertility in the male; urinary lithiasis and foreign bodies in the urinary tract, including the disadvantages of several methods used in stone analyses, and injuries of the genitourinary tract. Here, the reviewer does not share the author's opinion that blind litholapaxy is a dangerous procedure.

Almost 300 pages are devoted to an extensive review of the pathology, symptomatology, diagnosis and treatment of tumors of the urogenital system.

The treatment and pitfalls of neurogenic vesical dysfunction are presented in a succinct and didactic manner, and there is an excellent review of the innervation of and the pharmacologic effects of drugs on the bladder.

In a brief discussion of urology in the female, the author advocates the use of stylets to stiffen ureteral catheters. Many other authorities, however, feel that the use of stylets is dangerous and rarely indicated.

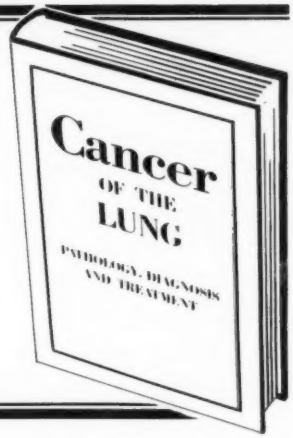
After a very well-written and informative summary of Campbell's "Pediatric Urology" comes a brief presentation of endocrinology as it concerns the urologist. Some of the topics of this section are discussed in more detail in a later section.

The material on preoperative and postoperative management of the urologic patient, anesthesia and urologic operations omits certain im-

*(Continued on page A-116)*

The first
comprehensive study of

# Cancer
## OF THE LUNG




**By MILTON B. ROSENBLATT, M.D.,** Assoc. Prof. of Medicine, New York Medical College; Visit. Physician and Chief of Chest Clinic, New York City Hospital, and

**JAMES R. LISA, M.D.,** Director, Pathology Service, Dept. of Hospitals, New York City; Director of Pathology Laboratories, Doctors Hospital, New York City.

This comprehensive work is devoted to all aspects of bronchogenic carcinoma—pathology, diagnosis, and treatment. It is designed to supply the physician in general practice with the latest techniques for early recognition and effective treatment. It will provide the specialist with essential, up-to-date, technical information on exfoliative cytology, bronchoscopy, resectional surgery and radiation therapy. In order to meet the challenge of early diagnosis, both early and atypical manifestations are described in detail. The various modalities useful in general palliative treatment and for relief of specific syndromes are fully discussed. Five chapters contributed by nationally recognized authorities, are—

*Bronchoscopy:* **CHEVALIER L. JACKSON, M.D.,** Prof. of Laryngology and Broncho-Esophagology, Temple University School of Medicine; Bronchoscopist, Temple University Hospital.

*Exfoliative Cytology:* **GEORGE N. PAPANICOLAOU, M.D.,** Prof. Emeritus of Clinical Anatomy and Director of Research, Papanicolaou Cytology Laboratory, Cornell University Medical College; and **N. CHANDLER FOOT, M.D.,** Prof. Emeritus, Surgical Pathology, Cornell University Medical College; Cons. Surgical Pathologist, New York Hospital; Consultant, Armed Forces Institute of Pathology.

*Surgical Therapy:* **J. MAXWELL CHAMBERLAIN, M.D.,** Att. Thoracic Surgeon, Roosevelt Hospital; Assoc. Visit. Surgeon, Chest Surgical Service; Bellevue Hospital; and **CHARLES F. DANIELS, M.D.,** Att. Thoracic Surgeon, Brooklyn Thoracic Hospital; Asst. Visit. Surgeon, Chest Surgical Service, Bellevue Hospital.

*Palliative Therapy:* **BERNARD ROSWIT, M.D.,** Chief, Radiotherapy Dept. and Director, Radioisotope Unit, V.A. Hospital, Bronx, N. Y.; Assoc. Visit. Radiologist, New York University-Bellevue Medical Center.

In preparing the balance of the book—Introductory Considerations, Prevalance, Pathology, Clinical Manifestations, Physical Diagnosis, The Roentgen Examination, Accessory Diagnostic Procedures, and Bronchial Adenoma—the authors have also had the assistance of ANGELO M. SALA, M.D., Assoc. Prof. of Pathology, New York Medical College; Pathologist, Metropolitan Hospital; former Pathologist, New York City Cancer Institute; and of HAROLD F. DORN, Ph.D., Chief, Office of Biometry, National Institute of Health.

Because the widespread public interest in cancer of the lung has been largely created by controversy on the subject, the authors have also included discussion of their own and other professional opinion on the smoking-lung cancer question.

Format 6⅛″ x 9¼″, 424 pages, 181 illustrations.

**SPECIAL PRE-PUBLICATION OFFER.** For a limited time only, advance orders for CANCER OF THE LUNG (published price $15.00) will be accepted at the special pre-publication price of $13.50. Copies at this reduced price are available directly from the publisher *only*, and should be ordered promptly.*

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portant procedures or illustrates them poorly. Although more detailed descriptions and illustrations would necessitate another volume, this would be acceptable so that the text could be considered a complete reference.

The role of irradiation in treating tumors of the urinary tract is handled concisely and precedes a discussion on hypertension, nephritis and medical diseases of the kidney in infancy and childhood—topics which appear too infrequently in urologic texts.

The last portion of the work includes a lucid description of the adrenal glands, their anatomy and normal and abnormal physiology. The role of adrenalectomy in hypertension, in malignancies of the breast and prostate, and in various endocrinologic and nonendocrinologic diseases of the adrenals is well presented. Adrenalectomy is described but Young's operation for simultaneous exposure of the adrenals is omitted, and the illustrations seem somewhat inadequate.

In spite of the criticisms mentioned, this is the most comprehensive work on urology in the English language and is a valuable addition to the library of the urologist. The binding, printing and illustrations are excellent.

M. P. R.

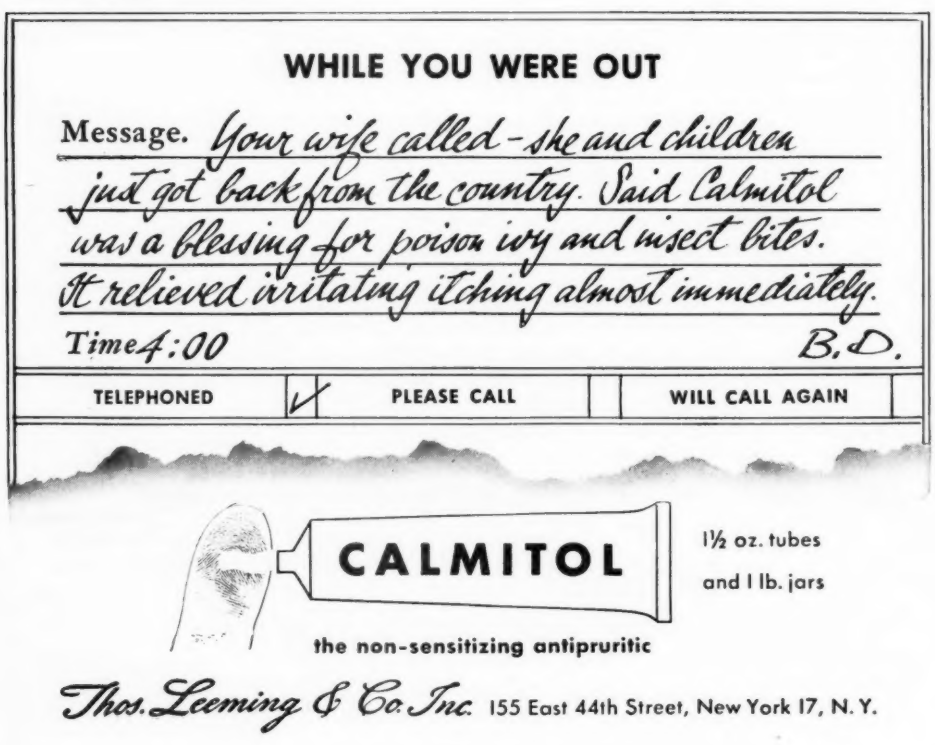
## ► PROGRESS IN ALLERGY

*Edited by Paul Kallós, from the Margareta and Erik Wihlborg Laboratory for Research in Allergy, Sweden. With nine contributors. Vol 4. 520 pages with 149 figures and 63 tables. 1955, Little, Brown & Company, Boston. $20.00.*

In this fourth volume, as in preceding volumes, the editor continues to bring together contributions of outstanding investigators from all over the world. It is not the purpose of the book to review every phase of allergy, but rather to present a selected group of current studies pertinent to the field. Each paper is an exhaustive study comprised of the author's own contributions and an extensive bibliography. Subjects in the present volume range from pathology through biochemistry, biosynthesis of adrenal steroids, intermediary metabolism and experimental asthma, to a final chapter on fungi of respiratory importance.

In the introduction Dr. Kallós previews the succeeding papers and helps to orient the reader by integrating the work represented with that of others in the particular field.

*(Continued on page A-118)*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**Is lymphstasis the pathogenesis of cancer?** Lymphatic obstruction edema has long been recognized as possibly a most important feature in the cause of neoplastic growths. In the new second edition of **THE GENESIS AND PREVENTION OF CANCER,** Dr. Handley reviews the pertinent literature, his research findings, and the results of other studies on the subject. The author, W. SAMPSON HANDLEY, M.S., London, FRCS, received in 1954 the Comfort-Crookshank Prize for cancer research. Specialists in cancer research and physicians in general practice will be interested in his book.

*Publication: May,*
*320 pages, illus., Prob. $4.00*

**What constitutes an abnormal finding?** The physician who wants the answers to his problems in everyday clinical activities, where biochemical principles are involved, will find **BIOCHEMISTRY OF DISEASE** of great merit. The second edition, by DR. OSCAR BODANSKY, is a systematic presentation of the biochemical aspects of the various diseases, arranged by clinical entities. All the significant qualitative and quantitative deviations found in disease are interpreted.

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*1,222 pages, illus., $12.00*

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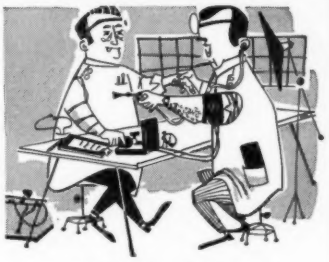

When you're sick or disabled, chances are your professional income stops. You've no boss to carry you on the payroll . . . no 30-day sick leave . . no workman's compensation.

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Milton Bohrod of Rochester, New York, reviews in a dynamic fashion the histology of allergic and related lesions, including those of infections and rheumatoid and collagen diseases, and stresses that an allergic lesion is an inflammatory response. He presents classifications of these lesions, correlated with various factors, to be used as a working basis for further study. A section on granulomas is of much interest.

R. L. Mayer of Summit, New Jersey, presents the allergic potentialities of the aromatic amines and nitro compounds which, among myriad uses, are the basis for many drugs and coloring agents. He traces the transformation products, formed by oxidation or reduction, to certain common intermediate compounds, thus explaining the tendency to cross sensitization to apparently unrelated substances.

Sidney Raffel of Stanford University discusses the delayed type of hypersensitivity reaction in infections and contact allergy and its possible role in tissue grafting and postvaccinal encephalitis. He demonstrates that this phenomenon must depend on the presence in the tissues of some factor in addition to the antigen and outlines various experiments which suggest that a lipoid substance may be the common denominator.

Gregory Pincus of Boston examines the role of the adrenal cortex in steroid synthesis, utilizing studies on steroid content of adrenal venous blood and steroid output of isolated perfused adrenal glands. The role of cholesterol is further substantiated by isotope technics. The evidence for an enzyme system also is outlined.

Frank Engel, Durham, North Carolina, details the functional interrelationships between the anterior pituitary and adrenal cortex in intermediary metabolism. He discusses stress diseases on this basis and presents in tabular form the different metabolic reactions to various combinations of stress, ACTH and cortisone.

Thomas Dougherty of Salt Lake City assembles the experimental evidence relating to three actions of the adrenocortical hormones, namely, antianaphylactic, antiphlogistic and antibody suppression. He concludes that despite evidence of some degree of antibody suppression, the beneficial effects of steroids in man cannot be explained on that basis. He believes that they moderate the allergic reaction primarily by a local antiphlogistic effect, and that their optimal use in disease will depend on adequate methods for estimating relative insufficiency and supplying the amount needed at a particular site.

IN ANXIETY AND TENSION

Sedation without hypnosis

IN HYPERTENSION

a safer tranquilizer and antihypertensive

Noelpp-Eschenhagen and Noelpp of the University of Zurich explain the details of their thoraco-abdominomotography technic for the study of experimental asthma, particularly in guinea pigs, and summarize their many observations. They also discuss the dynamics of respiration and analyze the various factors of breathing work in experimental asthma.

Kate Maemsell, London, discusses the role of fungi in respiratory allergy and outlines technics for study of this subject.

It will be seen from the foregoing that this is not a book for the physician only casually interested in allergy. On the other hand, it provides a wealth of reference material and much thought-provoking discussion for the investigator in any of the fields on which allergy impinges.

L. L. H.

## ► MANUAL OF HAND INJURIES

*By H. Minor Nichols, M.D., Clinical Instructor in Surgery, University of Oregon Medical School, Portland. 352 pages with 180 illustrations. 1954, The Year Book Publishers, Inc., Chicago. $9.50.*

The reviewer believes that this manual, which was written essentially for medical students, residents and practicing general physicians and surgeons, should be of particular aid to those who occasionally are called on to render first aid and initial definitive treatment to the injured hand. The book is well illustrated and concise. In some respects it may be too concise for those for whom it was written. For example, there is only one short paragraph on the preparation of the operative field. This, together with débridement of the wound and other measures used to prevent infection, is so important in the early care of hand injuries that more space could have been delegated to these measures. As pointed out by the author, many of the procedures mentioned or described are not recommended for the surgeon who occasionally operates on the hand.

The reviewer does not agree with the author about certain methods of treatment which are advocated; for example, the use of circumferential wire sutures for fixation of fractures and the excision of so-called aberrant tendons in De Quervain's stenosing tenosynovitis.

The author has purposely omitted a discussion of the merits of certain drugs. HYDROCORTONE® is so beneficial and its use has become so wide-

*(Continued on page A-122)*

FOR MAINTENANCE THERAPY

℞ as little as 0.1 mg. per day

Serpasil™

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a pure crystalline alkaloid of rauwolfia root first identified, purified and introduced by CIBA

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**more potent and longer lasting analgesia**

*than with morphine*

**less likely to cause constipation**

*than morphine*

**smaller dosage required**

*than with morphine*

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May be administered orally, subcutaneously,

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*relief of severe, intractable pain*

Addiction liability is the same as with morphine and the same precautions should be observed as with other narcotic analgesics. Narcotic blank required.

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Ad 873HL

...no two hypertensives are alike

**Tim Jones must stay on Rauvera**

***Diagnosis: Moderately severe, chronic, fixed hypertension; arteriosclerosis.***

T. J., nervous tense executive, used to be on Veratrum products, but the high dosage necessary to control his symptoms caused annoying nausea and occasional vomiting. Now he is doing well on Rauvera (1 tablet t. i. d. after meals). The ***combination therapy*** of 1 mg. alseroxylon and 3 mg. alkavervir per tablet of Rauvera is the best medication for him, because it reduces his need for Veratrum and successfully manages his Grade III type of hypertension.

On Rauvera his blood pressure dropped promptly, his headaches disappeared, his pulse rate slowed, he is in good spirits. No toxic effects were noted.

Rauvera® is a DORSEY preparation. Supplied in bottles of 100, 500, and 1,000 tablets.
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**Tim Jones must stay on Rauvera—for no two hypertensives are alike.**

spread that a brief discussion of indications and contraindications for its use would have been of special value in the chapter on "Degenerative diseases of peritendinous tissues."

In spite of the book's shortcomings, which are few, and all books have some, the crippling which is so prevalent because of mismanagement of hand injuries and infections of the hand probably could be reduced if this manual were required reading and a part of the library of those for whom it was essentially written.

P. R. L.

## ► ABDOMINAL OPERATIONS

*By Rodney Maingot, F.R.C.S., Eng. Surgeon to the Royal Free Hospital, London and to the Southend General Hospital. Ed. 3. 1,568 pages with 1,594 illustrations. 1955, Appleton-Century-Crofts, Inc., New York. $24.50.*

As the author states in the preface, the great advances made in abdominal surgery since publication of the 1948 edition made it necessary to revise the whole book drastically. He has tripled the number of contributors and thereby brings the reader authoritative material by eminent men interested in particular phases of abdominal surgery. The title might lead one not familiar with this book to consider it purely a treatise on technic. It is that, but in addition it gives an excellent presentation of symptomatology, diagnosis, pathology, laboratory aids, preoperative preparation, postoperative care and, particularly, possible complications and their management. These features make it attractive to all interested in abdominal surgery and especially to those in surgical training.

It is noteworthy that in a given situation Maingot gives his own preferred procedure and then gives alternate possibilities with reasons why they are preferred by other authorities. Also, in presenting results, he quotes widely from other surgical centers in addition to presenting his personal experience. These features give the advantage of a collective review on each topic.

The excellent illustrations of past editions have been retained and others have been added. The interesting historical notes have been retained and, as before, when reference is made to a key article in the literature the source is presented in parentheses—not hidden in a bibliography.

F. J. K.

*(Continued on page A-124)*

"THIOSULFIL"®
Brand of sulfamethylthiadiazole
safest, most effective sulfonamide
for urinary tract infections
The high degree of solubility of "Thiosulfil" combined with its high bacteriostatic activity and low acetylation rate insure rapid and effective action with virtually no side effects.
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. . . no two hypertensives are alike

**Julia Miller does well on Rautensin**

***Diagnosis: Hypertension Grade II, tachycardia***

J. M., active clubwoman, 55, has a moderately high blood pressure and a very rapid heart rate which have been considerably reduced after 35 days on Rautensin (mixed Rauwolfia alkaloids—the alseroxylon fraction) on a schedule of 2 tablets (4 mg.) daily, taken at one time before retiring. Now Julia is much calmer and happier than all last year. Later on she will probably do well on a 1 tablet (2 mg.) daily maintenance dose. No postural hypotension and only minor side effects (stuffy nose) have been observed.

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*TRADE MARK

**Julia Miller does best on Rautensin—for no two hypertensives are alike.**

## ► ANTIBIOTICS AND ANTIBIOTIC THERAPY

*By Allen E. Hussar, M.D., Chief of Medical Service, Franklin Delano Roosevelt Veterans Administration Hospital, Montrose, New York and Howard L. Holley, M.D., Associate Professor of Medicine, Medical College of Alabama, Birmingham. 475 pages. 1954, The Macmillan Company, New York. $6.00.*

There have been a number of small books dealing with individual antibiotics, as well as journals devoted to these products. This appears to be the first authoritative clinical manual which evaluates progress in this rapidly advancing field during the last decade.

The first 54 pages establish the fundamentals of antibiotic therapy, using the term introduced by Waksman in 1941. There are discussions of factors influencing the mode of action, correlation between in vitro sensitivity and clinical use, and the indications and complications of antibiotic therapy, with final stress on "The 12 commandments." This section has 154 references.

The second part contains a general description of the antibiotics in clinical use. As expected, there is a detailed consideration of penicillin, with 143 references. This is followed by briefer discussions of streptomycin, AUREOMYCIN®, TERRAMYCIN®, tetracycline, chloramphenicol, bacitracin, polymyxin, neomycin, tyrothricin, erythromycin and CARBOMYCIN®. A brief bibliography supplements each of these sections.

Part 3, "The drug of choice," stresses the clinical phase in a series of discussions of bacterial infections and diseases, rickettsial and viral infections, and fungal and parasitic infections and diseases. Under each disease, the relative values of the various antibiotics are emphasized, including considerations of methods of administration, frequency and duration of doses.

The authors then present a discussion from the clinical standpoint with respect to customary infections in the specialized fields, including pediatrics, surgery, obstetrics, gynecology, otolaryngology, ophthalmology, urology, dermatology and dentistry. The sensitivity of the various organisms in these specialized areas is indicated as the basis for proper selection of antibiotics.

There is an 11 page subject index to aid in the proper use of the book. The authors are to be congratulated on the results of their extensive studies as consolidated herein. The reviewer would suggest in a revision of the book that it would be more helpful if the references in the various bibliography lists were arranged in alphabetical order, rather than by order of their appearance in the text.

J. C. M.

**Books received will be acknowledged in this department each month. As space permits, books of principal interest to our readers will be reviewed more extensively.**

**Pain; Its Mechanisms and Neurosurgical Control.** By James C. White, M.D., Associate Professor of Surgery, and William H. Sweet, M.D., Associate Clinical Professor of Surgery, Harvard Medical School, Boston. 736 pages with 134 illustrations and 53 tables. 1955, Charles C Thomas, Springfield, Illinois. $17.50.

**Casimir Funk; Pioneer in Vitamins and Hormones.** By Benjamin Harrow, Emeritus Professor of Chemistry, City College, New York. 209 pages. 1955, Dodd, Mead & Company, New York. $4.00.

**Should the Patient Know the Truth?** Edited by Samuel Standard, M.D., Associate Professor of Clinical Surgery, New York University College of Medicine, New York, and Helmuth Nathan, M.D., Assistant Professor of Surgery, Albert Einstein College of Medicine, New York. With 23 contributors. 1955, Springer Publishing Company, Inc., New York. $3.00 (hard cover), $2.00 (soft cover).

**Ion Exchange and Adsorption Agents in Medicine;** The Concept of Intestinal Bionomics. By Gustav J. Martin, Sc.D., Research Director, The National Drug Company, Philadelphia. 333 pages with 26 illustrations. 1955, Little, Brown and Company, Boston and Toronto. $7.50.

**A Textbook of Physiology.** Edited by John F. Fulton, M.D., Sterling Professor of the History of Medicine, Yale University School of Medicine, New Haven. 12 contributors. Ed. 17, revised. 1,275 pages with 600 illustrations. 1955, W. B. Saunders Company, Philadelphia. $13.50.

**Tell Me Doctor.** By Henry B. Safford, M.D., Professor Emeritus of Obstetrics and Gynecology, New York Medical College, New York. Ed. 2. 256 pages. 1955, Hawthorn Books, Inc., New York. $3.95.

**Antibiotics Annual 1954-1955;** Proceedings of the Second Annual Symposium on Antibiotics. Edited by Henry Welch, Ph.D., Director, Division of Antibiotics, Food and Drug Administration, U.S. Department of Health, Education and Welfare, and Felix Marti-Ibañez, M.D., International Editor of *Antibiotics & Chemotherapy*. 1,150 pages, illustrated. 1955, Medical Encyclopedia, Inc., New York. $10.00.

**Differential Diagnosis of Internal Diseases.** By Julius Bauer, M.D., Clinical Professor of Medicine, College of Medical Evangelists, Los Angeles. Ed. 2. 940 pages, illustrated. 1955, Grune & Stratton, Inc., New York and London. $15.00.

**. . . no two hypertensives are alike**

**Joe Smith is on Crystoserpine**

***Diagnosis: Emotionally disturbed; labile hypertension Grade I***

J. S., greatly agitated individual, is now on Crystoserpine (crystalline reserpine-Dorsey), 1 tablet of 0.25 mg. q. i. d. because he is emotionally disturbed, nervous, ambitious but often frustrated. His work means unrelenting pressure, and as a result he developed a mild, labile hypertension (Grade 1). After three weeks of therapy he is a calm, tranquil individual. His blood pressure and slightly elevated pulse rate are down to normal. At no time did Crystoserpine cause postural hypotension or toxic effects. Now his family can "live" with him.

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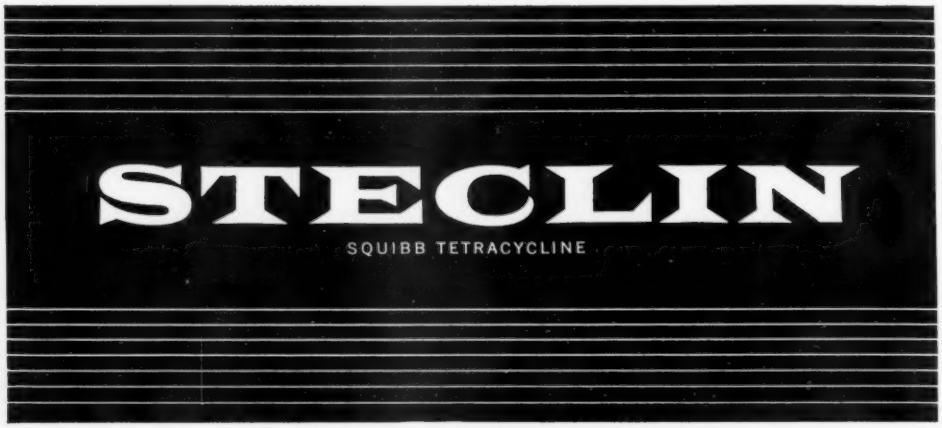


promptly reaches high levels in the urine

crosses the intact meningeal barrier more readily than the other broad spectrum antibiotics

produces higher blood levels than the other broad spectrum antibiotics

less gastrointestinal side effects than the other broad spectrum antibiotics

*Minimum adult dose:* 250 mg. q.i.d.
250 mg. capsules, bottles of 16 and 100.
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*Each FULL-STRENGTH tablet contains:*

Phenobarbital ..... 15.0 mg. (¼ gr.)
Methscopolamine bromide ..... 2.5 mg.

*Dosage:*

One tablet one-half hour before meals, and 1 to 2 tablets at bedtime.

*Each HALF-STRENGTH tablet contains:*

Phenobarbital ..... 8.0 mg. (⅛ gr.)
Methscopolamine bromide ..... 1.25 mg.

*Dosage:*

While the dosage and indications are the same as for the full-strength tablets, this tablet allows greater flexibility in regulating the individual dose, and may be employed in less severe gastrointestinal conditions.

*Supplied:*

Both strengths in bottles of 100 tablets.

*REGISTERED TRADEMARK FOR THE UPJOHN BRAND OF METHSCOPOLAMINE

**The Upjohn Company, Kalamazoo, Michigan**

# DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

**Apr. 1**—Back to the desk with a mass of letters and the problem of the two medical societies which do not like the plan for immunizing the youngsters against polio. Also Evelyn Mayer came with problems of decorating and Pepys talked to Hans Selye in Montreal and Paul Warwick in New York. In the evening to the Blackstone where the Chicago Junior Association of Commerce and Industry honored Ernest Irons for his outstanding citizenship. Under his leadership the Municipal Tuberculosis Sanitorium has become a leading institution, free from racketeering, free from a long waiting list, and cooperative with all other agencies. So old Pepys greeted Jim Hutton, Julius Hess, Ed Piszek and George Lull with his staff from the A.M.A., and he sat with the Kellys and had a fine evening.

**Apr. 3**—Early awake and went to our new home where all came to celebrate Justin's birthday which is April 7 and moved many delicate lamps and paintings to the new quarters. Thereafter to play at "Scrabble" at the Friedells' and returned with Mistress Pepys to the new domicile.

**Apr. 4**—Early came Stanley Henwood to discuss the proceedings of the International Poliomyelitis Congress. At noon to sit with Bundesen, William Fishbein, Henrichs, Heckel, Jones and the advisory committee from the Chicago Medical Society and tried to resolve the controversy over the administration of the polio vaccine, but little came of it except a flood of oratory such as I have seldom heard, and in such a fever heat wise decisions are never reached. So old Pepys left to take the B & O Capitol Limited and read the last half of "Sincerely, Willis Wade" by Marquand, a story well and truly told, full of insight into human motivations and provocative of chuckling at its sly humor.

**Apr. 5**—At noon to the White House, shaking hands with the President who greeted warmly the advisory board of the American Korean Foundation. Old Pepys was happy to greet again Jim Kerrigan, Volwiler, Barney, McKeen, Howard Rusk, Frank Wilson, Fitzgerald, Driscoll, Fischelis—altogether about 30—and the luncheon and the whole occasion were memorable.

**Apr. 6**—At my writing until noon when W. S. Middleton of the Veterans' Administration and George Lyon came to luncheon at the Mayflower. Here we talked of new research and reminisced about the great medicos who came from Wisconsin—Hektoen, Billings, Murphy, Dodson and many more. And Middleton has done a biographic study of them. Thereafter to the airport to fly to New York and the weather was so fearful that I left the hotel at 3:00 P.M. and reached New York at 7:00 P.M. so that I could just as well have walked. On the plane was former Governor Dewey and apparently no one noticed him, but as we deplaned a man said to his little daughter: "Look, honey, that man once ran for president of the United States." After dinner to see Marlon Brando in "On the Waterfront" and with it Judy Holliday in "Born Yesterday," both well worthwhile.

**Apr. 7**—Early to Doubleday for conferences with my editors—Beebe and Lees. Next came Parmele and Alden James for a visit. In the evening to Lindy's with Mark Soroko where Dr. William Stoltz was eating matzos. I told Lindy that I had had lunch with the President. "What did they serve?" he asked. Next out to Rose Soroko's family where a real old-fashioned Seder was under way and drank some cherry wine from Denmark. Thereafter out to Milton Lasdon's for gin rummy.

**Apr. 8**—To Doubleday for a long conference with Josephine Lees and finally completed the marriage book. At another meeting with Paul Warwick, Baldwin, Welsh and Mosely and others of the staff until noon contemplating a research program. For two hours with Mel Evans and associates outlining a new book and then by American Airlines to Chicago. En route read Gaddis' "The Recognitions," which is hundreds and hundreds of pages of stream of consciousness and introspection and symbolism. At the airport come Mistress Pepys and Z. W. and went home to catch up on the mail.

*(Continued on page 130)*

# from rigidity to relaxation

When the rigidity and pain of arthritis and related rheumatoid disorders prevent the patient from enjoying a normal, satisfying life, Acetycol may open a road to rehabilitation. Therapy with Acetycol provides welcome relief of pain and increases the range of pain-free movement. Thus the patient is able to resume more normal activities in his work and relaxation.

The effectiveness of Acetycol is based on synergism between aspirin and para-aminobenzoic acid. The combination of these two agents produces high salicylate blood levels on relatively low dosages. Salicylated colchicine extends the effectiveness to cases of a gouty nature.

Acetycol also contains three essential vitamins often lacking in older patients: ascorbic acid, to prevent degenerative changes in connective tissue; thiamine and niacin, for carbohydrate utilization and relief of joint pain and edema.

*Usual dosage—1 or 2 tablets three or four times a day.*

*Each Acetycol tablet contains:*

| | |
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| Aspirin | 325.0 mg. |
| Para-aminobenzoic acid | 162.0 mg. |
| Colchicine, salicylated | 0.25 mg. |
| Ascorbic acid | 20.0 mg. |
| Thiamine hydrochloride | 5.0 mg. |
| Niacin | 15.0 mg. |

**Supplied:** Bottles of 100 and 500.

# Acetycol

TRADEMARK

*to relieve rheumatic pain*

**WARNER-CHILCOTT**

**Apr. 9**—Now in a temporary apartment working all day and in the evening resting with television.

**Apr. 10**—Composing editorials and watching the lake in its changing moods. Later came the children to Easter dinner which Mistress Pepys composed honoring Barbara Friedell's birthday, and this gave great joy to Rosemary. So contributed to Friedell in mathematical games at which he is better than good.

**Apr. 11**—With the mail and in conference with the decorators. Then with Mistress Pepys to catch the train for Ann Arbor, Michigan, and met Phil Lewin and Howard Shaughnessy. Dining all together and Lewin showed exceptional skill in gin. At the Michigan Union saw all the newshawks and the scientists. Here were Tommy Francis, Tom Parran, Tom Turner, Ken Landauer, Art Snider, Roy Gibbons, Bob Kleckner, Bill Laurence, David Dietz, Harry Weaver, Van Riper, Kumm and many more. With the Van Ripers for late coffee and doughnuts. And so to bed.

**Apr. 12**—To breakfast with Dietz and Kleckner and greeting Ken Maxcy and his lady, Gustavson, Henry Viets and many others. Then to Rackham Hall where Murrow and Dave Garroway were holding interviews and there were dozens of motion-picture cameras and TV machines and old Pepys took colored stereos of Salk and the family and Basil O'Connor with Tommy Francis. And all this truly came from O'Connor's leadership. So the report of the effectiveness of the Salk vaccine was made and old Pepys watched how John Paul and Sabin listened. It seemed that every speaker was uttering gems, for the occasion was itself brilliant. And old Pepys contemplated that it took 10 years for Semmelweis' great discovery to filter out to the world. And now all the world was waiting breathlessly for the results of one of the greatest studies ever made and performed in the field of preventive medicine.

So next to a luncheon at the Michigan Union where we sat with Deans Sevringhaus, Caughey, Whittaker and Houston Merritt and we heard the Michigan

*(Continued on page A-132)*

METICORTEN

PREDNISONE (metacortandracin)

Schering

more potent than cortisone
or hydrocortisone · devoid of
major undesirable side effects

*T.M.

METICORTEN,* brand of prednisone.

# *Safer Combination Therapy*

## IN

# HYPERTENSION

## Rauwiloid® + Veriloid®

in a single tablet

Indicated in moderately severe hypertension. Each tablet contains 1 mg. Rauwiloid and 3 mg. Veriloid.

Initial dosage, one tablet t.i.d., p.c. Available in bottles of 100 tablets.

## Rauwiloid® + Hexamethonium

in a single tablet

Indicated in rapidly progressing, otherwise intractable hypertension. Each tablet contains 1 mg. Rauwiloid and 250 mg. hexamethonium chloride dihydrate.

Initial dosage, one-half tablet q.i.d. Available in bottles of 100 tablets.

- SIMPLER THERAPY—Simplified dosage regimen, simplified dosage adjustment, and easier patient management.
- GREATER SAFETY—GREATER EFFICACY—Under the synergistic influence of Rauwiloid, the potent antihypertensive agents act with greater efficacy at lower, better tolerated dosages, and with notable freedom from chronic toxicity.
- BETTER PATIENT COOPERATION—In each instance, only one medication to take . . . hence easier-to-follow dosage instructions.

***More Convenient for the physician . . .***
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Glee Club, which is one of the best, and a talk by President Hatcher which was a classic. So home by the N. Y. C. with Carey McCord, Franklin Ebaugh and Packard and Harry Weaver and Phil Lewin—a trip of rare fun and rejoicing.

**Apr. 13**—To the desk answering calls from near and far about the vaccine—a topic in the minds and thoughts of everyone.

**Apr. 14**—At noon J. R. Wilson came to lunch to talk of his new work with such food industries as Armour and BiB and wondering what path the A.M.A. Councils, of which George Simmons and Frank Billings and Torald Sollmann were so proud, will follow now. In the evening to cocktails at the Hotel Sherman where the Hektoen Institute held its annual meeting. Dan Ryan, president of the County Board, presided; Karl Meyer and old Pepys spoke to the distinguished audience. Sam Hoffman made the arrangements. Old Pepys inducted the officers of the Woman's Auxiliary. The new mayor, Daly, came and expressed his interest. Old Pepys talked of new research with Dick Young and Arthur Colwell of Northwestern and Harry Dowling of Illinois, and the wealthy citizens wrote checks inspired by the story of Salk's vaccine.

In 1860 the editor of the Louisville *Journal* published his wisecracks under the title "Prenticeana." Here are a few selections:

"The Chinese have succeeded in producing a new and delicious variety of tea. We suppose they have accomplished this by crossing their teas."

"It is very well that the youth of our country should get high, but they should do so as the oaks do—by drinking water."

"Place confers no dignity upon such a man as the new Missouri senator. Like a balloon, the higher he rises, the smaller he looks."

"Those periodicals are most likely to explode which haven't a spark of fire in or about them."

---

**Apr. 15**—Busy rounding up the moving and clearing my desk.

**Apr. 16**—To the Museum of Science and Industry to view the science fair and amazed at the wonderful exhibits of the high school children. Young Friedell has designed an electronic computer which solves geometric problems. In the evening to dine with my brother Albert and then to the train.

**Apr. 17**—In Syracuse met by Charles Haney and Dr. George Gibbs and drove to Seneca Falls. First we toured the Seneca Falls and Waterloo hospitals, two man-

*(Continued on page A-134)*

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sions of ancient vintage now converted into hospitals, and one with a new elevator which would be the safest place to be housed in the hospital. Thereafter to speak to some 800 residents in behalf of a new hospital, meeting Drs. Allen, Smith, Towers and all the ladies. Then driving back to Syracuse with the Middletons for dinner at the Onondago in honor of their first anniversary and presented them with Canning's "A Handful of Silver," which is a fine mystery.

**Apr. 18**—In New York and spent the morning with Josephine Lees and Ralph Beebe on new book projects. At noon to luncheon where came Beebe and Evans for still more conference. Next talking to Welsh and Parmele and Harry Berk and for dinner with Herb and Grace Mayes to the Stork Club where Sherman Billingsley presented the ladies with perfume. Thereafter to George Marek's for bridge with him and Richard Frey with great fun and great luck.

**Apr. 19**—Early awake for breakfast with Will Craft as always cheerful. Then again to Doubleday. For noon luncheon came Therese Rivers, the Runyons and the Van Ripers and most of the talk about the vaccine. In the afternoon to talk with Frank Egner, Richard Frey and Landsberger about new publications. In the evening came Bill Lasdon, Milton, Stanley and all the ladies, and with Elmer Bobst and Governor Driscoll and with Professor and Lily Alivisatos to cocktails and then to dine merrily at the new Embassy Club of Serge Obolensky in the Ambassador on beef stroganoff.

**Apr. 20**—For breakfast came Elmer Bobst to talk of many plans, in particular the Atlantic City dinner of the Silver Slipper Club. Then to lunch with Mark and Rose Soroko and off to the sailing of the Queen Elizabeth. For the good-by party the Runyons, Beebes, Henwoods with Barton, Alden James, Johnny Kirsch, Therese Rivers—and a fine day. This evening played bingo and Mistress Pepys won.

**Apr. 21**—Lay late and then to my scrivening. At the table of Dr. Rust are Victor Gollancz, argumentative British publisher, and his lady, Stephen Potter, distinguished author and editor, Medhurst, surgical supply maestro of Hull in northeast England, and Pepys with Mistress Pepys. Reading Ruark's "Something of Value," a tough novel of the outrages by both natives and whites in Kenya. The movie "Captain Lightfoot" is a costume romance of Ireland without distinction except for the scenery. In the evening Mistress Pepys won three straight times with a double ticket on the horse races. What a lady to have along!

**Apr. 22**—Read "Maigret in New York" by Simenon and wrote letters and won 100 points in a "Scrabble" game. Then saw "Deep in My Heart" about the life of Sigmund Romberg which is two hours or about twice too long. Played bingo and missed by one number three times. No comment.

**Apr. 23**—Again late in bed reading "He Ought to Be Shot," which is nothing much. Played "Scrabble" and saw a movie, "The Day His Number Came Up," a frightening British production which would terrify anybody unaccustomed to airplane travel. For cocktails in the observation lounge with Dr. Spigel of Norfolk chatting about the Kaufmans and Prices and other mutual friends. For dinner a sort of gala production ordered by Gollancz with five kinds of liquor, beef broth with sherry, fillet of sole with Château Yquem, veal cutlet and vegetables with Burgundy, chunks of pineapple in ice cream with spun sugar, and a sweet Tokay, and then choice of cordials. Next to the horse races and missed three times by a nose.

**Apr. 24**—Finished reading "Two Tickets to Tangier" by van Wyck Mason who has a formula for Captain North. Writing many letters and played gorgeously at bridge with Mrs. Martin of Cincinnati against Dr. and Mrs. Joseph Gaye of Philadelphia. Next saw "Simba," a movie about the Mau Mau which tells in one hour of film all that Ruark really has to say. At night most unsuccessful at bingo and started a history, "From Lexington to Liberty" by Bruce Lancaster.

Doctor (to nervous patient): Have you ever awakened suddenly with a jerk?

She: Why, doctor, I'm not even married.

---

She was a great big dame in the middle forties and she kept moving around in the middle of a crowded bus. Said the man next to her: "Madam, will you lift yourself off my foot."

"Why don't you put your foot where it belongs," she said.

And he answered, "Madam, don't tempt me."

---

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Postgraduate Medicine

# Nutrition and Disease

*Special Issue from the*

DEPARTMENT OF NUTRITION AND METABOLISM,
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CHICAGO, ILLINOIS

NUTRITION CLINIC, HILLMAN HOSPITAL,
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HOSPITAL GENERAL CALIXTO GARCIA, HAVANA, CUBA

HOSPITAL MIMIYA, SANTURCE, PUERTO RICO

*Guest Editor: TOM D. SPIES, M. D.*

*NUTRITION*
*and*
*DISEASE*

●

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### Acknowledgments

The investigations reported briefly here have been supported by many philanthropic foundations, persons and corporations. The Nutrition Foundation aided in many of the studies. The Williams-Waterman Fund aided in training several of the physicians who are contributors. The Clayton Foundation for Research aided in the studies for the prevention of physical disabilities. The C. F. Kettering Foundation aided the work done in Chicago. Fundación de Investigaciones Clínicas aided in the work in Puerto Rico. For a few years Fundación de Investigaciones Médicas aided in the work in Cuba.

# FOREWORD

Articles appearing in this issue of POSTGRADUATE MEDICINE are the logical outgrowths of scientific studies initiated over two decades ago. Application of our knowledge of nutrition has not only stopped the ravages of pellagra in this country, but has made endemic sprue virtually nonexistent in Cuba and Puerto Rico. These accomplishments have been spectacular, but more far-reaching and fundamental have been the understanding and extended use of all aspects of nutrition.

That this rapidly expanding field of medical science will have a profound effect upon geriatrics is a foregone conclusion.

The constant increase in world population makes the problem of adequate food ever more pressing. Hunger is a common concern and one which knows no national boundaries. Fortunately, like other matters of health, it is one problem where international cooperation is natural, logical and effective.

This is particularly emphasized by the cooperative effort of Dr. Tom D. Spies and his staff, with Dr. Ramón M. Suárez, Sr., Dr. Guillermo García López and their associates in Puerto Rico and Cuba, respectively.

Their impressive record accomplished with a relatively small amount of money should focus the attention of the world upon the enormous future possibilities of this branch of medicine.

J. ROSCOE MILLER, M.D.
*President, Northwestern University*

# NUTRITION and METABOLISM

The science of nutrition and metabolism is young, but vigorous. A recent survey by the Food and Nutrition Board of the National Research Council reports that approximately 4800 projects, 660 organizations conducting or supporting research, and about 5000 professional research workers are engaged in food and nutrition research. Approximately 40 per cent of the research projects pertain to nutrient metabolism and requirements, 30 per cent to food chemistry and composition, 20 per cent to food technology and 10 per cent to microbiology, food acceptance and nutrition education.

Many advances in medicine in the next fifty years will be derived from refinement of technic, new knowledge and better and wider application of findings in the field of nutrition, food technology and metabolism. Not only will there be advances in the scientific aspects of these fields, but, also, far-reaching social and economic contributions. The recent era of meticulous assaying of foods for specific nutrients and the establishment of crude signs and symptoms of deficiency diseases will give way to microbiologic and chemical technics to detect subclinical deficiency states, establishing of chemical profiles of normal individuals and those with so-called degenerative diseases and more accurate information on the metabolic aspects of intracellular life and its optimal supporting environment. The alarming food-population problems of the world may gain some relief through the fascinating possibilities of production of proteins from algae, yeast and fungi and the cultivation of insects to produce protein foods for animals.

To establish itself as an exact science each discovery in this field has followed the traditional route of medical advances, initial doubt and incredulity, enthusiasm replete with fads and fancy, overenthusiasm with overextending of a scientific observation, reaction of discreditation and finally sound basis and clinical research and realistic application. Dr. Spies and his associates have been leaders in the field taking discoveries from the laboratory, demonstrating their application clinically and developing standard technics for diagnostic appraisal and group therapy which are efficacious and practical no matter whether it be in the Midwest, the South or the Caribbean. Dr. Spies has fostered the basic concepts of "nutritional failure" and that disease is primarily chemical and chemically correctable. Subclinical nutritional deficiency states must exist and only await for their detection sufficiently accurate methods of chemical diagnosis.

The contributions of Dr. Spies and his associates to this special issue devoted to the subject of nutrition and research reflect their wide experience in teaching and research and thus constitute a fundamental guide to the physician.

RICHARD H. YOUNG, M.D.
*Dean, Northwestern University Medical School*

# INTRODUCTION

From time to time in the past quarter of a century we have presented evidence that to be well, man must eat properly. We have shown that what he eats has much to do with his health and even with his recovery from ill health. Our goal, like yours, is optimal nutrition, but as yet we do not know just what that is. We do know that the dietary constituents are the stuff of which tissues are made. We know that from conception tissue growth, tissue maintenance, and tissue repair depend on the availability of adequate quantities of essential food factors.

As physicians, let us face a number of our difficult problems. Disease is as old as living matter. The cells of the human body, like all other living things, must adapt, grow and reproduce. By the time a person has reached maturity, he perhaps has had a thousand diseases, which he has overcome. The cells of the body are composed of atoms which are here today, and tomorrow or soon thereafter return once more into the remainder of the world. No cell of the body remains unchanged, and our external environment likewise is unstable. As physicians, we search perpetually to better the situation, and all too often we fail. Our bodies and our personalities result from the structure of our tissues. We have been at least 500 million years in coming to our place as the highest of all the vertebrate families. Of all living creatures, only man can serve as philosopher, physician and investigator, and can attempt to shape the world to his heart's content. From time eternal, man has tried to ease his pain, to relieve his disabilities, and to discriminate between the foods that are good for him and those that are not. We contend that illness is chemical; therefore, man must achieve biochemical independence before he can go further.

As young physicians 25 years ago, we had a strong conviction that scientific problems should arise in the mind of the medical investigator from his experiences in the clinic. We knew that to aid the practicing physician, we had to work on the problems as they were presented to him. Because of our interest in chemistry and in what has come to be the science of nutrition, our objective became one of devising methods for aiding every sick person who came to us and for whom no specific therapeutic remedy was known.

The burdens and tragedies arising from the disabilities of acute and chronic diseases are immeasurable. The ill person is lost in a world he never made. The patients used as illustrations came to us in what we term a biochemical crisis. Many of these patients were sent from practicing physicians, who at that time could not help them. As medical investigators, we consider ourselves merely as aids to the practicing physician in maintaining the health of

his patient. The physician and the investigator must have a spirit of unity, and research must lead to fruitful and lasting results.

So much of the field of nutrition relating to the treatment of the sick has been allowed by default to the faddist, the home economist and the radio broadcaster. Among some groups of patients it is likely that more than 50 per cent could be helped by proper dietary advice. The public badly needs guidance from trained physicians in how to obtain better health through better nutrition.

In the present-day practice of medicine we often apply therapy the nature of which little is known. Our working concept is that health is the accurate, harmonious and constant integration of all the necessary biochemical factors in the body. The amino acid balance, the vitamin balance, the endocrine balance, the electrolyte balance, the control of body temperature, the maintenance of blood glucose level, and the supply of oxygen to the cells are a few of the important factors. Ill health may result from a derangement of these or any other biochemical system which disturbs the harmony of the cells. Prolonged ill health may result from sudden trauma, acute infections, or even from disturbance of mental processes. Associated with the emotions are many biochemical phenomena. Fear may produce syncope; sadness may produce excessive lacrimation; and anger or joy may cause insensitivity to pain. The state of mind, therefore, can alter body functions. Body and mind must work together continuously and are mutually dependent. The normal outcome of a harmonious relationship is health.

On the early perception of any source of disharmony depends the success of preventive medicine. By the time the characteristic physical signs of a disease are observed, the tissues already have been badly damaged. Accordingly, the physician should attempt to develop insight into the biochemical action within the cell in order to have knowledge of living processes. The mechanism of action may be unknown, but he should not fall into the error of thinking it is unknowable. It is a formidable undertaking to initiate this concept but it must be undertaken.

The authors have prepared this issue of POSTGRADUATE MEDICINE to aid those physicians who would like to foster their interest in nutrition. The physician must remember that to rely entirely on dietary therapy is inadvisable and impractical. Deprivation of essential food constituents exists in the tissues for a long time before lesions develop, and it is essential to give intensive therapy in order to restore health promptly. Dried brewer's yeast powder and liver extract are excellent therapeutic agents for the treatment of diseases arising from a deficiency of the B complex vitamins. These substances contain a significant amount of protein and many essential nutrients. They are indeed useful in prevention and are now widely used as supplements.

From day to day the practicing physician naturally wonders just what he can count on in the scientific world of changing uncertainties. The very essence of achieving gratifying results is an accurate diagnosis, and for that reason we will present many pertinent illustrations.

An apparent paradox makes teaching the diagnosis of deficiency states difficult indeed. The so-called classic case is, in fact, the rare case. The so-called atypical case is the usual case. This strange situation arose because the lesions of certain individuals are much more spectacular than are those of others. In every instance the disease, whether typical or atypical, is the response of the tissues to prolonged deprivation of essential chemical substances. All patients respond promptly to adequate and persistent therapy. The patient with classic lesions may be an advanced case or he may be an early case. The patient in either an atypical or a classic case can die from lack of proper therapy. In all cases the general considerations are the same. The lesions are so specific in etiology that there is no way of treating them except by supplying the missing chemicals. It matters not to the patient or his welfare whether the manifestations of his disease are classic, but his health and frequently even his life itself depend on the physician's recognizing the lesions and prescribing adequate and persistent therapy.

# oral symptoms and signs OF NUTRITIONAL DEFICIENCY

The old-fashioned physician frequently inspected the mouths and tongues of patients but could offer them little in specific diagnosis or therapy of their deficiency syndromes. In the past 25 years more than 70 per cent of the patients we have seen with clinical evidence of deficiency diseases have had some abnormality of the tongue, gums or buccal mucous membranes. To successfully treat patients with pellagra, scurvy, sprue, pernicious anemia, iron deficiency or other related diseases the physician must recognize the changes of nutritional origin which affect the oral cavity. These syndromes are not rare; in most instances failure of diagnosis occurs because many physicians fail to consider them or are unwilling to make a diagnosis unless all the classic signs are present. Such classic signs are uncommon and nearly always are associated with the late stages of the disease. Early recognition followed by specific treatment eliminates a great deal of the morbidity and mortality.

There is no specific laboratory test for any of these syndromes. Diagnosis must depend chiefly on a reliable history and a careful physical examination. In procuring the history the physician should bear in mind that pellagra, scurvy and other primary deficiency syndromes are particularly prevalent in the following three groups:

1. The indigent, and those with erroneous dietary habits or idiosyncrasies. Such persons tend to eat diets relatively high in carbohydrate and fat and low in protein and vitamins over long periods of time. Their diets tend to lack lean meat, fish, eggs, milk, fresh fruits and vegetables. Such persons may have an endemic form of disease.

2. Persons with organic diseases. Symptoms and signs suggestive of these deficiency syndromes are frequent among persons with diseases of the alimentary tract, liver, heart and kidney, and with diabetes mellitus, dysenteries, parasitic infestation, tuberculosis and malaria. The majority of these persons, even though undernourished, do not have the diagnostic clinical lesions. They have what is termed secondary nutritional deficiency disease.

3. Persons with chronic alcohol addiction. Those who consume large amounts of alcohol and do not eat an adequate diet are prone to develop deficiency diseases.

Irrespective of predisposing or precipitating factors, the lesions, symptoms and specific methods of treatment are the same.

Certain diagnostic tongue lesions should trigger us into making a proper diagnosis of pellagra even though the classic skin lesions and dementia are absent. Physicians who are unfamiliar with pellagra sine pellagra or pellagra sine eruptione may be perplexed when the only physical manifestation is involvement of the tongue. Pellagra is classified as endemic, alcoholic or secondary. The latter, pellagra secondary to organic disease, is particularly important today because many young physicians have had little experience in observing lesions arising as a result of a primary disease. Often they are unaware that deficiency of certain members of the vitamin B complex may result in lesions of the tongue and mouth. Not infrequently in various medical centers, when visiting ward patients with organic disease, it is possible to detect a mild glossitis that previously had not been recognized.

## Case One

A 27 year old white man had had good health until six months before we first saw him, when he broke his leg and was in a hospital for 18 weeks. During this time pain, worry about finances and his family, and apparent dislike of hospital food contributed to a loss of appetite. He ate candy and desserts brought to him by friends but rarely ate anything from his hospital trays. For about two weeks before he left the hospital he noticed soreness and burning of his tongue. After he went home the soreness gradually increased, and it was difficult for him to eat. His tongue became fiery red, and white patches appeared on the undersurface.

# *pellagra*
## AND SECONDARY VINCENT'S INFECTION

He consulted a dentist who diagnosed Vincent's infection and prescribed mouth washes, but his tongue became worse. When he was brought to us, we observed that the underlying problem was pellagra (figure 1). We administered 500 mg. of nicotinamide orally daily in divided doses and the glossitis promptly disappeared. Figure 2 shows his tongue a week after treatment was initiated. He became rehabilitated and served in the air force during World War II.

Comment—Secondary pellagra may appear in the terminal stages of diseases upon which it is ingrafted, or following trivial diseases or accidents. This patient was well until a traumatic injury forced him to be hospitalized. It would appear that his food intake was inadequate and that the amounts of nicotinic acid amide and tryptophan available from it were too small, resulting in a nutritional imbalance. Finally the deficiencies became translated into recognizable lesions and a diagnosis was made. It was obvious for some time that this man had serious malnutrition before secondary pellagra was diagnosed. The disappearance of the Vincent's infection, which was secondary to the nicotinic acid amide deficiency, is typical following the administration of nicotinic acid or any suitable salt of nicotinic acid.

Chemically, niacin or nicotinic acid is termed 3-pyridine carboxylic acid, and niacin amide is termed 3-pyridine carboxylic acid amide. The crystals of nicotinic acid arrange themselves as shown in figure 3; figures 4 and 5 show the structural formulas of nicotinic acid and its amide.

Figure 1

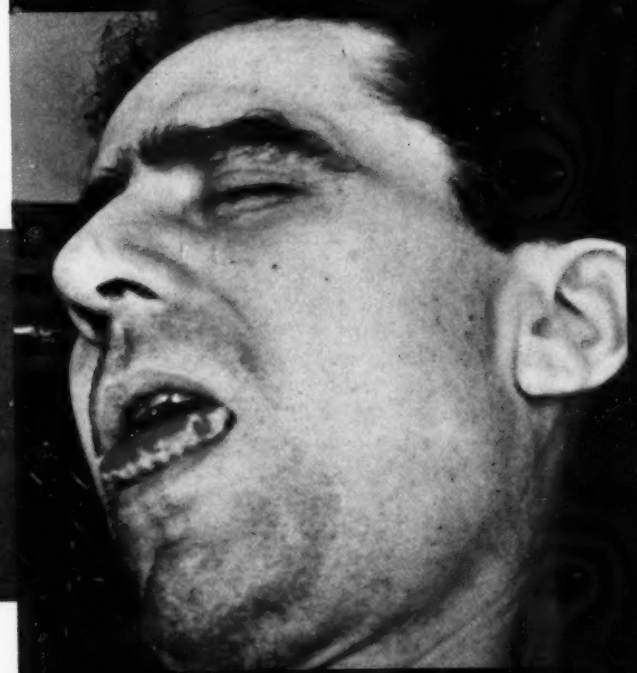


Figure 3

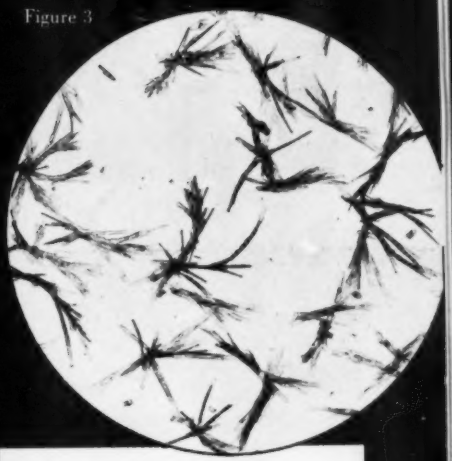
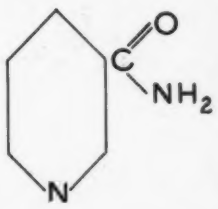
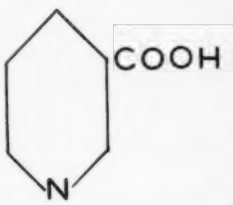


Figure 4




NICOTINAMIDE

Figure 5




NICOTINIC ACID

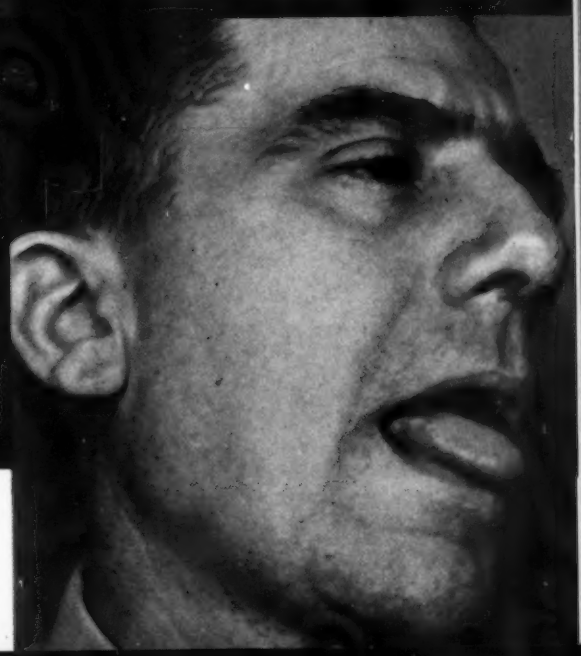


Figure 2

# scurvy INFANTILE TYPE

## Case Two

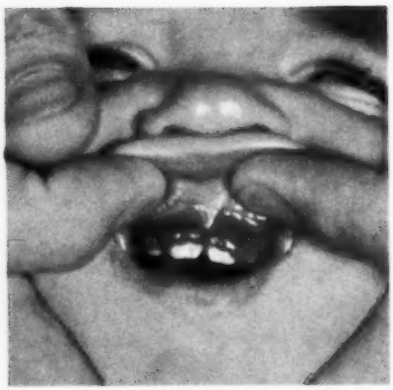


Figure 6

Figure 7

A 10 month old white infant was breast-fed until he was one month old, when his mother's supply of milk became so scanty that he was weaned and given a formula of evaporated milk, KARO® syrup and water, supplemented with cod liver oil. When he was four months old, his mother began to offer him orange juice, cereal and egg yolk daily. He took his food fairly well until he was five months old, when bronchitis developed, he lost his appetite and became a difficult feeding problem. He refused all foods except his formula, lost weight and became pale. When nine months old he began to cry and fret almost constantly and screamed when his mother tried to feed him. She noticed that his breath was fetid and his gums were red and sore. A physician prescribed a mouth wash but the infant's gums became worse. He could no longer pull himself to a standing position in his crib or let himself down. In the following two weeks he was taken to several physicians, but despite the therapy they prescribed he steadily became worse. When he was brought to us he had a high fever, hematuria and an increased pulse rate. There was no ascorbic acid in the plasma. The severe gingival reaction of scurvy around the teeth can be seen in figure 6. The lesions appear characteristically swollen and dark red in color. Figure 7 shows his gums 96 hours after the daily administration of 150 mg. of ascorbic acid in his formula. Note that the gums appear almost normal in tone and color. Two teeth which were almost buried by swelling are now clearly visible. The fever, increased pulse rate and pallor promptly subsided after treatment was initiated.

A 56 year old Negro woman had eaten a high carbohydrate diet all her life, but until her husband's death she had eaten fresh fruits and vegetables frequently. After his death (a year before we saw her) her income became so small that she felt she could not afford them. Her gums had been sore for about three months when she first consulted a dentist, who treated her for Vincent's infection for several weeks without relief before he referred her to us. When we saw her, the condition of her mouth was serious (figure 8) and she had a high fever. There was no ascorbic acid in the plasma. We gave her 1000 mg. of ascorbic acid orally in divided doses within 12 hours. Figure 9 shows her mouth 24 hours after treatment was initiated. As can be seen, there already was a profound change. On the following day her temperature was normal, and within two months she obtained work as a housemaid. She corrected her diet, and in the past 12 years she has had no specific therapy and there has been no evidence of scurvy or Vincent's infection. Figure 10 shows her mouth at present.

Comment (cases 2 and 3)—Most cases of scurvy in infants are seen in those who are artificially fed, although we have seen it in breast-fed infants whose mothers have had a restricted diet. The florid type of gum involvement seen in case 2 is rare. Subacute scurvy with less gum involvement but often with greater tendency to petechial hemorrhages and swollen and tender thighs is more common, but most common of all is the latent type with its vague and indefinite symptoms and difficulty of recognition. Whatever the type or grade, rapid improvement follows specific therapy, and this, in an infant, resolves itself into including an adequate amount of ascorbic acid in the diet.

Scurvy in adults tends to occur past middle life, and particularly affected are bachelors or persons living in prison camps or homes for the indigent. Months of ill health precede the characteristic lesions. Treatment demands first the removal of the cause, followed by an adequate diet containing sufficient ascorbic acid.

# *scurvy*

## ADULT TYPE

### Case Three

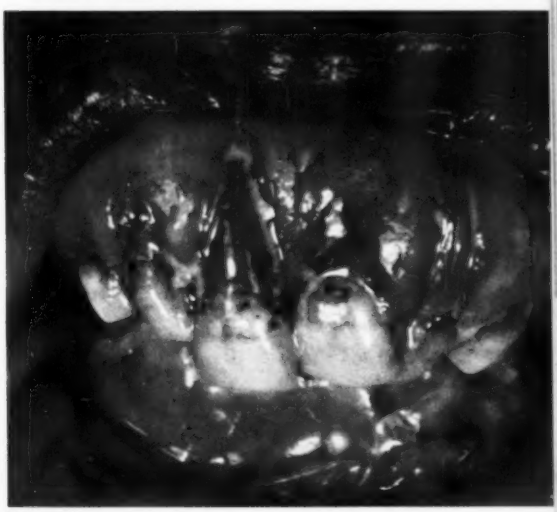


Figure 8

Figure 9

It is noteworthy that the ascorbic acid had disappeared from the plasma in both case 2 and case 3, yet both cases were diagnosed on clinical examination as scurvy by the appearance of the gingival tissue. The problem of diagnosing subclinical deficiencies remains one of the most important for medical scientists of today. We have observed many patients with no ascorbic acid in their plasma but no symptoms of scurvy. We believe important information on vitamin C status can be obtained by determining the concentration of ascorbic acid in the blood plasma. On the average it is found that this is much lower in our patient group than in our normal controls. Of course, it is well known that the ascorbic acid content of the white cells may remain fairly high even though there is no detectable ascorbic acid in the plasma.

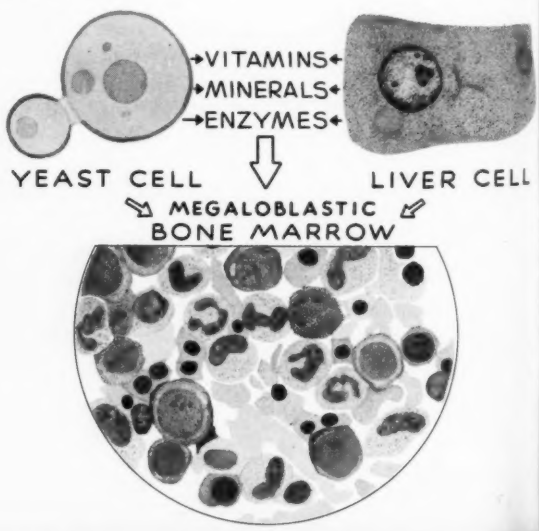
By this time it certainly must be realized that any disease can predispose to the development of pellagra or scurvy or other deficiency states by altering the patient's relationship to his external environment. As an investigative group, we have longed to understand as much as possible about the regenerative processes of cells. For 25 years we have made studies of yeast, liver and bone marrow cells, our hypothesis being that if we could understand fully their chemistry it would help us immeasurably to understand the megaloblasts. Figure 11 illustrates certain relationships that now have been demonstrated between these cells in which we have special interest. Twenty-five years ago, scientists visualized the total effect of the vitamin B group in liver and yeast as due to a single substance. It is clear that they placed too narrow a significance on the effect of liver and yeast, for we already know they contain 17 important entities which play an important role in general physiologic processes.

Figure 11 shows in a diagrammatic way how we are trying to meet the challenge of restoring the function of the tissues of our patients. We know the diagnosis of nutritional deficiency disease is extremely difficult, and that it is not easy to distinguish between symptoms arising from a deficiency of vitamins and those arising from an underlying organic condition. We have not been willing to accept the so-called "minimal daily requirement" for nutrients. We consider such a recommendation a ridiculous assumption and one to which, as physicians, we should not adhere blindly.

Soon after nicotinic acid and ascorbic acid came into rather general use, physicians began to refer to us cases which they thought were related to scurvy or pellagra but which would not respond to either nicotinic or ascorbic acid. Our wide clinical and laboratory experience made it possible for us to diagnose these cases and gradually to devise better methods of treatment. Many of these patients had diseases of the tongue or alimentary tract or bone marrow or skin, and we naturally thought there might be something in yeast or liver capable of producing a remission.

Figure 10

Figure 11



# blacktongue

## Case Four

Figure 12 *top;* Figure 13 *lower left;* Figure 14 *lower right*

This is a term applied to a naturally occurring disease in dogs, cats and man. The disease in man seems to have no etiologic relationship to blacktongue in dogs or to the less well-known blacktongue in cats. Blacktongue in man does not respond to niacin therapy, whereas canine and feline blacktongue disappears when the animal is adequately treated with niacin or substances which act similarly. An example of blacktongue in man is shown in figure 12. A lesion such as shown here is the result of a fungus growing on the tongue, and it is not affected by administration of niacin. Certain antibiotics given over a long period of time may predispose to the development of blacktongue in man. There is no known nutritional remedy available at this time.

Pets eating scraps from the tables of persons who eat a pellagra-producing diet naturally tend to develop similar chemical deficiencies in their tissues. Deficiency of niacin or substances which act similarly may produce lesions such as those shown in figures 13 and 14. Blacktongue in dogs primarily involves the mucous membranes, and the ulcerations tend to be filled with Vincent's organisms. Note the well-demarcated ulcerations of the mucous membrane of the dog (figure 13). Blacktongue in cats, at least in the early stages, tends to involve primarily the point and tip of the tongue (figure 14).

Comment—With the disappearance of endemic pellagra in the southeastern part of the United States, the disappearance of canine and feline blacktongue also has been noted. This is a striking example of how the health of animals has improved as a result of nutritional investigations.

For centuries inspection of the tongue has played a part in the art of diagnosis, but only recently have serious attempts been made to investigate the normal and abnormal appearances of the tongue's surface and to provide a photographic record of such appearances. Observations of characteristic changes in the mucosa of the tongue in the presence of various deficiency diseases have led us to repeated inspection of the tongue in order to detect signs of malnutrition.

Although the cases presented thus far emphasize the importance of nutrition in everyday diagnosis and therapy, the significance of changes in the oral tissues deserves still more consideration. Changes in the color of the lips and the oral and pharyngeal mucosa often are sensitive indicators of systemic disturbances and may exist long before more severe signs and symptoms appear elsewhere in the body. In the control of dental caries, the most prevalent disease of childhood and adolescence, many lesions are overlooked. Dental caries, periodontal disease, and artificial dentures present special problems and will be discussed briefly.

Many physicians, pediatricians and dentists do not fully appreciate the role of the fermentable carbohydrates in the dental caries process. Many physicians caring for the aged do not fully appreciate how periodontal disease and artificial dentures may reduce the efficiency of natural dentition, nor do they realize that many artificial dentures have little more than cosmetic value. Nutritional deficiency states decrease the ability of the supporting tissue to adjust to artificial dentures. Many nutritional problems in older persons are either directly or indirectly related to inadequate mastication resulting from poorly constructed or poorly fitting dentures.

# nutritional macrocytic anemia

Case Five

For over 60 years a 70 year old white man had eaten a diet consisting chiefly of corn bread, biscuits, grits, salt pork and cereal. He rarely ate meat, milk or eggs. He had periods of weakness, dizziness and shortness of breath which were often associated with diarrhea and a sore tongue. He had had bouts of diarrhea of several weeks' duration during the spring and fall. When he came to us he had had diarrhea for several weeks and was having 8 to 12 liquid, brown stools in 24 hours. He had dermatitis of mild pellagra. His tongue was intensely red (figure 15) and he had a severe macrocytic anemia with a red blood cell count of 2.21 million and a color index of 1.25. His bone marrow showed megaloblastic arrest. An oral glucose tolerance test showed a flat curve, and there was free hydrochloric acid in the gastric juice. Physical examination showed no evidence of spinal cord involvement.

Administration of 100 mg. of nicotinic acid orally five times a day for a week gave him some increase in strength and vigor, but his clinical response was not maximal; no change occurred in the blood values during the week of treatment or in the following week. He was then given massive doses of crude liver extract, and on the fourth day his appetite and strength increased, the reticulocytes increased, and subsequently the red blood cells and hemoglobin increased. On the sixth day his tongue was much less red (figure 16). He was advised to eat liberal amounts of meat and eggs. Within two and a half months he returned to full-time work as a tinsmith. He has continued to eat a liberal, well-balanced diet, has had no recurrence of symptoms and at 80 years of age still can work.

Comment—Nutritional macrocytic anemia coexists endemically with many other vitamin B complex deficiencies. The condition occurs frequently in the southern part of the United States, in Cuba and in Puerto Rico. It is similar clinically to pernicious anemia, and the two conditions often cannot be differentiated without careful observation. It is most important, however, to determine whether the primary difficulty results from the diet or from a deficiency of the intrinsic factor in the patient's stomach. This man, for example, has had 10 additional years of work by correcting his diet and without receiving specific treatment; this is in contrast to what might be expected in addisonian pernicious anemia.

Patients with nutritional macrocytosis are usually elderly, and careful questioning will disclose a diet deficient in animal protein—little or no lean meat and too little eggs and milk. Symptoms and signs of chronic pellagra, beriberi and riboflavin deficiency are common. Blood and bone marrow findings are indistinguishable from those of true pernicious anemia, and oral glucose tolerance curves are flat. Gastric juice is moderately abundant and usually contains free acid.

Figure 15

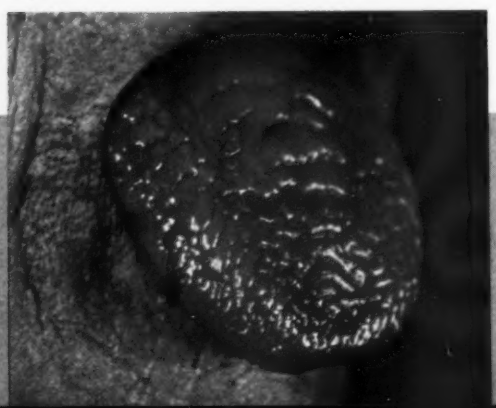


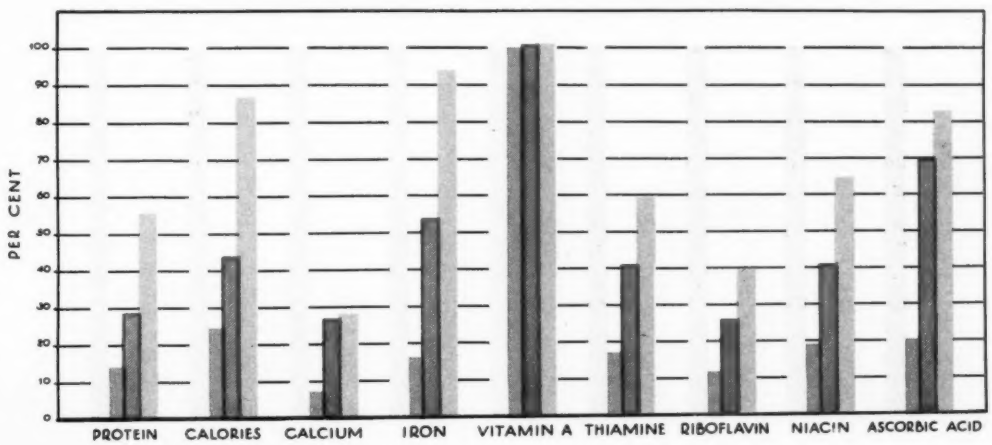
Figure 16

# nontropical sprue

A 58 year old white man had been diagnosed by his physician as having pellagra and treated with nicotinic acid without benefit. When he was referred to us we learned that his diet was typical of that eaten by persons with endemic pellagra (figure 17); for many years it had consisted almost exclusively of corn bread, salt pork, grits and syrup. He never ate green vegetables or fruit and rarely ate meat or eggs or drank milk. He complained of loss of appetite and strength, diarrhea, abdominal cramping, and inability to eat because of soreness of the tongue. His tongue was red and slick (figure 18). He was having 8 to 10 copious, liquid, yellowish-white, foul-smelling stools in 24 hours. The gastric juice contained abundant free hydrochloric acid, and an oral glucose tolerance test showed a flat curve. His stools contained no parasites, ova or blood. His red blood cell count was 2.10 million, hemoglobin 54 per cent. Bone marrow was essentially normal. We made a diagnosis of nontropical sprue and gave

Figure 17

NUTRIENTS SUPPLIED BY DIET BEFORE AND AFTER FOLIC ACID THERAPY.




ALLOWANCE OF NUTRIENTS RECOMMENDED BY COUNCIL ON FOODS AND NUTRITION, NATIONAL RESEARCH COUNCIL.

NUTRIENTS SUPPLIED BY DIET OF PATIENT PRIOR TO THERAPY.

NUTRIENTS SUPPLIED BY DIET OF PATIENT SECOND DAY OF THERAPY.

NUTRIENTS SUPPLIED BY DIET OF PATIENT THIRD DAY OF THERAPY.

him 10 mg. of folic acid orally daily for three weeks. Within 48 hours after folic acid was initiated the stools became much firmer and normal pigments began to appear, as can be seen in figure 19 (the top portion of the bowel movement shows a beginning response to therapy). When folic acid therapy was discontinued after 21 days, the red blood cell count was 4.53 million and the hemoglobin 97 per cent.

Clinical improvement began on the second day of therapy, with beginning relief of the diarrhea and abdominal cramping and increased appetite (figure 17). He soon began eating large amounts of food and gaining in body weight. By the tenth day of treatment the stools were normal. In the three weeks he gained 13 pounds. He was instructed to eat a liberal diet, high in protein foods and green vegetables, and was allowed to go home. The following day he went back to work on his farm. He has followed the dietary instructions, has had no recurrence of symptoms, and has not missed a day's work in the past seven years.

Figure 19

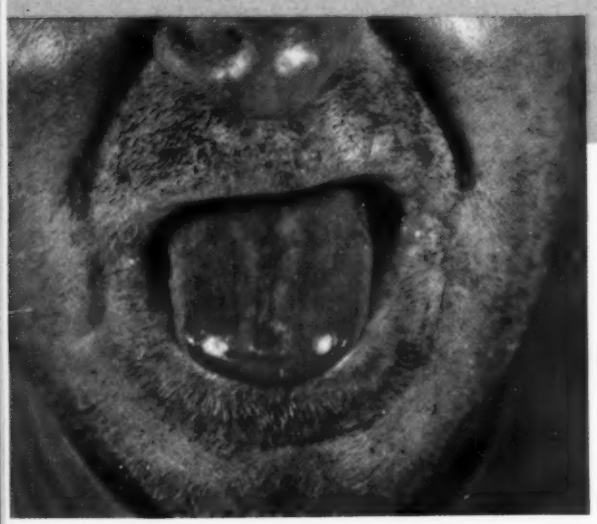


Figure 18

Comment—Cases of sprue, such as this, and spruelike conditions occur in the northern part of the United States but are not common. Many times the complicating features are so predominant that they overshadow the fundamental disorder with the result that it goes unrecognized. The stool in this case helped greatly in explaining the symptomatology. In many cases, however, symptoms arising from the alimentary tract are insignificant.

## Case Seven

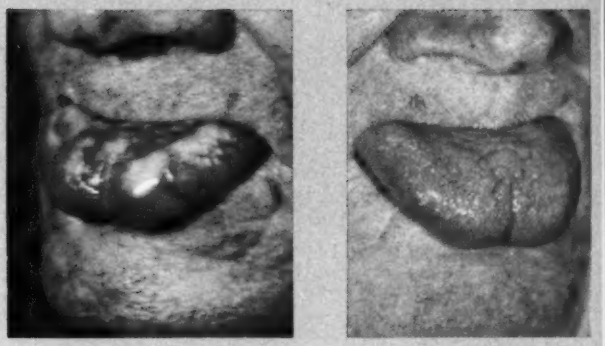


Figure 20

A well-nourished white man, 58 years of age, came to us because of recurrent glossitis. Large areas of his tongue were fiery red (figure 20, left); it was very smooth and in some areas almost purple. His grandfather had died of pernicious anemia. Except for his tongue, physical examination showed no abnormality. Repeated gastric analyses showed histamine-refractory achlorhydria. Blood values were normal. He was given 10 mg. of folic acid orally daily for 10 days, and his tongue became much better. He then was given a single 1 cc. intramuscular injection of refined liver extract. A great upsurge of strength and sense of well-being resulted and he returned to work. He continued to eat an excellent diet, as he always had. Within three months the glossitis recurred but was less severe than before. He was given 10 µg. of vitamin $B_{12}$ intramuscularly daily for four days, and relief of the glossitis was dramatic. He has received vitamin $B_{12}$ parenterally at intervals and has continued to work. The slick, denuded areas have been replaced by normal-appearing papillae (figure 20, right). On each examination he has continued to have histamine-refractory achlorhydria.

Comment—The great majority of patients with vitamin $B_{12}$ deficiency usually are not seen by a physician until they have developed anemia. In some instances they can be very ill without anemia; some 10 per cent of our patients have little or no anemia when the presenting symptom is a sore tongue. We call these "pernicious anemia sine anemia" patients. It seems likely that some might develop anemia if not treated. However, the response to treatment is prompt and full.

*recurrent glossitis*

CONSTANTLY RECURRING
HISTAMINE-REFRACTORY
ACHLORHYDRIA

Case Eight

# idiopathic hypochromic anemia

Figure 21

Figure 22

A 32 year old white woman, the mother of three children ranging in age from one to three years, came to us complaining of such great fatigue that she was unable to care for her husband and children without help. Her fatigue began with an acute respiratory infection six months previously, and although the infection cleared in two weeks, fatigue persisted and became increasingly more severe. Several members of her family had had pellagra and she thought that she too might have it. For many years her diet had consisted chiefly of corn bread, grits, biscuits, salt pork and syrup. She had eaten vegetables about once a week, lean meat and an egg about once a month, and had drunk buttermilk occasionally.

Physical examination showed a thin woman of asthenic build with a considerable increase in hair growth on the arms and face. Her tongue

Figure 23

was very pale (figure 21). There was pitting edema of the ankles (figure 22). She had "spoon nails" (figure 23); note the central spoonlike concavity with flat lateral edges and the everted ends of the nails. All fingers were affected to varying degrees, but the thumbs and forenails showed the most pronounced changes. Repeated gastric analyses showed hypochlorhydria. Her peripheral blood values were (figure 24): red blood cells 3.79 million; white blood cells 3,970; hemoglobin 8.7 gm. (57 per cent); reticulocytes 2.9 per cent. A blood smear showed many small red blood cells. The bone marrow was hyperplastic with a predominance of normoblasts; no megaloblasts were found. The plasma proteins were reduced to 4.1 gm. per cent.

She was given 600 mg. of ferrous sulfate orally three times daily for 42 days, then 300 mg. three times daily for 36 days, and she was advised to eat a diet containing liberal amounts of meat, eggs, milk and green vegetables.

Within two weeks the glossitis and pitting edema of her ankles had disappeared, and her fatigue was relieved. Her blood values increased (figure 24), her plasma protein level returned to normal, and she gradually gained in strength. During the last three weeks of ferrous sulfate therapy, she also was given 10 mg. of folic acid orally daily with no detectable effect on blood regeneration. Although the "spoon nails" are still visible, she has had no recurrence of her other symptoms in the past two years; her health has been excellent, and she has been able to take care of her home and her family.

Comment—The pallor, koilonychia ("spoon nails"), and the history were suggestive of idiopathic hypochromic anemia. The ferrous sulfate was effective in this case, and we have found, of course, that iron alone will relieve a deficiency of this metal in the body. This woman's muscular strength and sense of well-being increased so much that after two and a half months she returned to hard manual labor in the fields, and by our treating her from time to time, she has continued to work and feels fine.

Treatment of this type of anemia is not difficult unless the patient is hypersensitive to iron. In such cases, we cut down the dosage but continue treatment for a long time. In almost all instances a satisfactory dosage can be worked out so that the patient can be relieved and still have no alimentary tract distress.

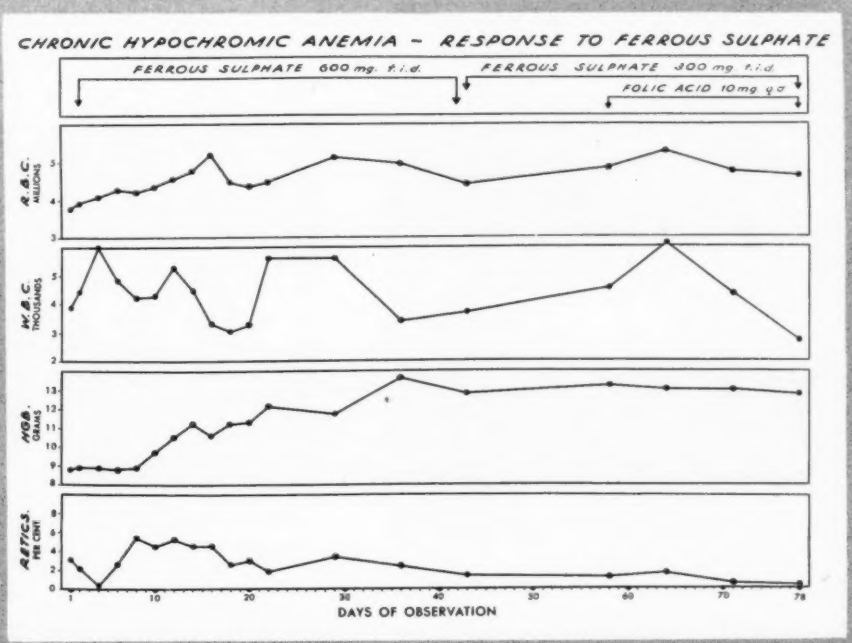



Figure 24

Case Nine

# pernicious anemia

## IN RELAPSE

Figure 25

A 52 year old white man with pernicious anemia who had been under observation and treatment for 10 years had a relapse because he became "tired of taking injections." His general symptoms were weakness, nausea, sore tongue and occasional bouts of diarrhea. His gastric juice contained no free hydrochloric acid even after histamine stimulation. His red blood cell count was 2.56 million, the color index was 1.3, and the bone marrow showed megaloblastic arrest typical of macrocytic anemia in relapse.

A long fissure extended through the skin and deep into the tissue of his lower lip (figure 25, top). This lesion developed without any known preceding trauma. In the period of three months during which it was observed, this fissure did not heal; it became slightly worse, as did his general condition. He was given 15 gamma of vitamin $B_{12}$ orally daily, with no hemopoietic or clinical response or change in the lip lesion. He then was given 15 gamma of vitamin $B_{12}$ combined with 100 mg. of intrinsic factor concentrate for 21 days. The hematologic response was striking (figure 26). His appetite increased greatly (figure 27), and the fissure immediately began to heal. The lower photograph in figure 25, taken after 15 days of therapy with vitamin $B_{12}$ and intrinsic factor concentrate, shows healing. This is the first demonstration of the therapeutic efficacy of vitamin $B_{12}$ in healing such a tissue lesion.

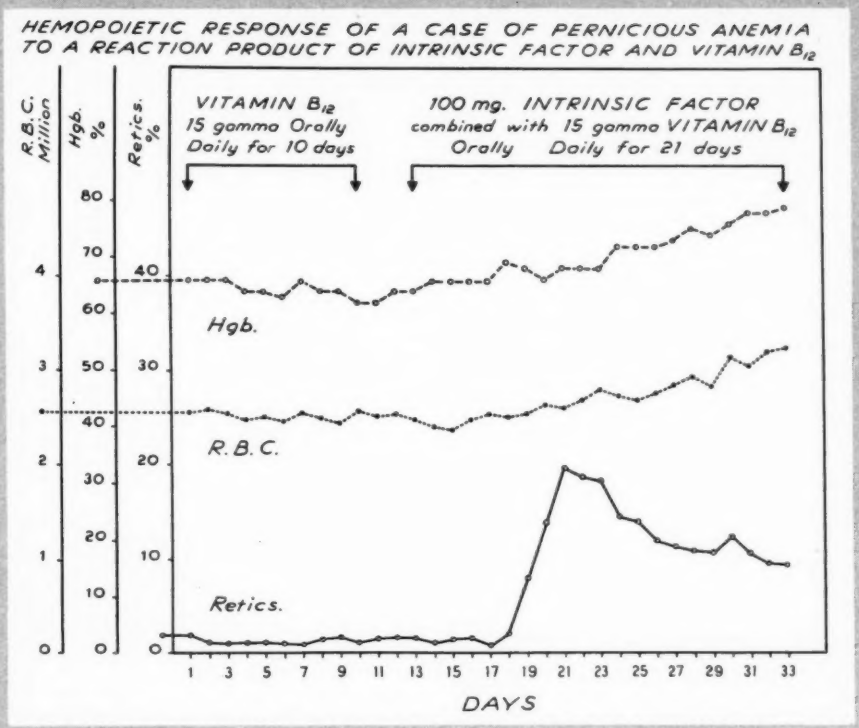
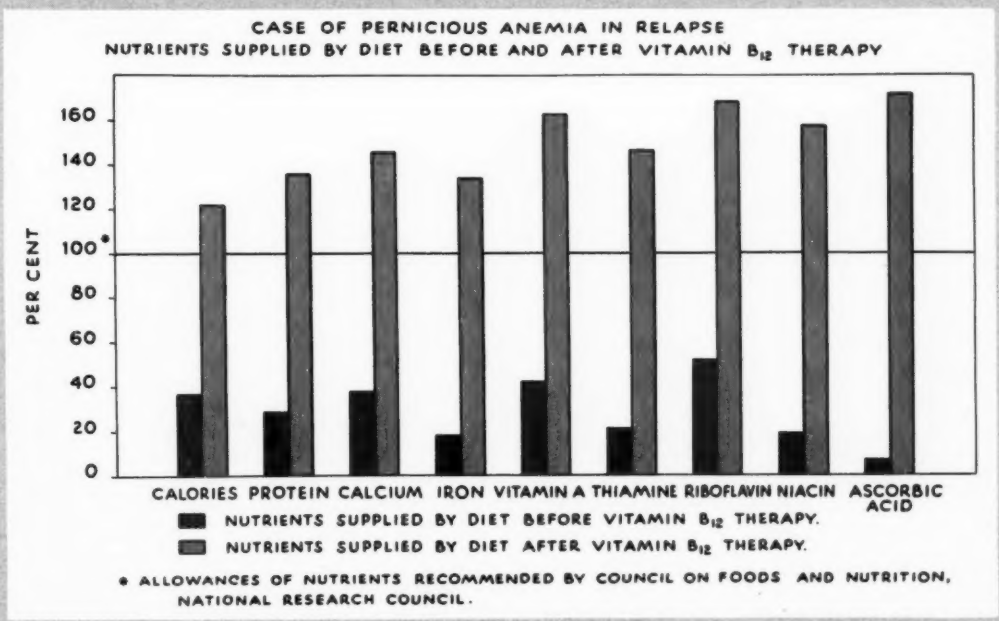



Figure 26

Figure 27


CASE OF PERNICIOUS ANEMIA IN RELAPSE
NUTRIENTS SUPPLIED BY DIET BEFORE AND AFTER VITAMIN B12 THERAPY
PER CENT
CALORIES PROTEIN CALCIUM IRON VITAMIN A THIAMINE RIBOFLAVIN NIACIN ASCORBIC ACID
NUTRIENTS SUPPLIED BY DIET BEFORE VITAMIN B12 THERAPY.
NUTRIENTS SUPPLIED BY DIET AFTER VITAMIN B12 THERAPY.
* ALLOWANCES OF NUTRIENTS RECOMMENDED BY COUNCIL ON FOODS AND NUTRITION, NATIONAL RESEARCH COUNCIL.

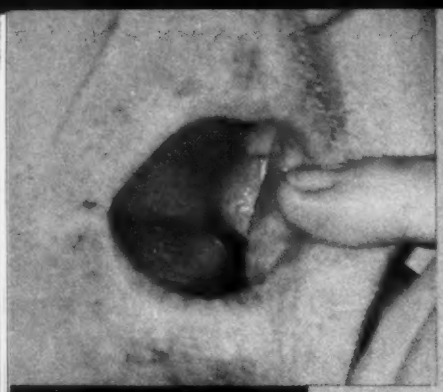


Figure 28

## Case Ten

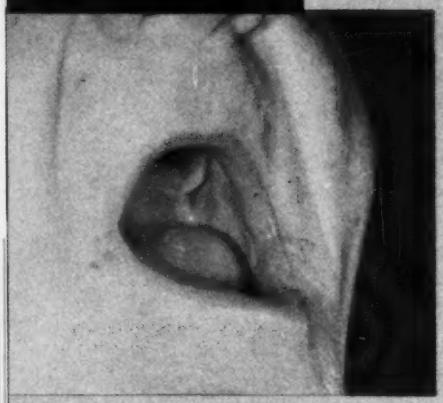


Figure 29

# stomatitis and pharyngitis

## DUE TO LACK OF VITAMIN $B_{12}$

A 72 year old white man has vitamin $B_{12}$ deficiency and gets a "sore mouth and throat when I am not treated." On more than a dozen occasions we have noted this red color appear (figure 28) and have seen it relieved either with the injection of a few micrograms of vitamin $B_{12}$ or by the administration of a potent intrinsic factor preparation and vitamin $B_{12}$. (Oral administration of vitamin $B_{12}$ alone in the amount of 15 μg. per day will not relieve the condition.) Following treatment there is a great upsurge in strength, vigor and appetite. Figure 29 shows the area of involvement after treatment has become effective.

Comment (cases 9 and 10)—More than 10 per cent of our patients with pernicious anemia show as the presenting sign and symptom involvement of the mucous membrane of the tongue, mouth or throat. If they are properly treated at this stage, neural degeneration and megaloblastic arrest do not appear or, if already present, do not progress.

Perlèche (meaning to lick), or angular cheilosis, as it has come to be known, is a condition marked by lesions occurring at the corners of the mouth. Usually bilateral, although not infrequently unilateral, the lesion tends to become triangular in shape and follows the skin fissures. In the acute stage the angles remain wet and macerated, frequently with an adherent yellow crust. The lesions may remain indefinitely, may heal, or may come and go. Angular cheilosis is associated with four conditions:

1. A decrease in the vertical dimension of the face produced when incomplete or ill-fitting dentures allow the facial muscles to sag, or when dentures settle due to alveolar resorption; deep fissures develop at the angles of the mouth.

2. A local infectious process or one due to toxic conditions. It is well known that yeast and other fungi contribute to perlèche, and we have shown that the involved areas frequently contain hemolytic staphylococci and streptococci. This type of lesion sometimes appears following the administration of antibiotics.

3. A deficiency of nutrients. The relation of riboflavin to the experimental induction of cheilosis was first demonstrated by Sebrell and his associates.

4. A manifestation of allergies. This may be part of a local or generalized response.

The relative degree of importance of mechanical factors, infections and lack of nutrients varies from case to case, and in many all may be involved.

A 61 year old white man was referred to us by his physician for diagnosis and treatment of lesions at the angles of his mouth. Ten years previously, alveolectomy had been performed on the lower ridge. Complete resorption of the ridge resulted, and his dentures did not even come close to restoring the vertical dimension. Soreness and cracking at the angles of his mouth developed three years before we first saw him. Physicians and dentists consulted on several occasions prescribed various types of therapy which gave no relief. The photograph in figure 30 was taken when we first saw this patient and shows the striking involvement at the corners of the mouth and the redness of the tongue. Secondary symptoms had developed because he had not been able to eat well. Correct vertical dimension was restored by the use of "bite blocks" in temporary dentures. The mandible was restored to correct relationship by new dentures, and the wrinkles and skin fissures were eliminated. Within three weeks the lesions healed (figure 31), his vague symptoms disappeared, and he had a desire to eat.

Comment—Persons with symptoms arising from decreased vertical dimension and poor dental function regularly respond to the construction of well-fitting, complete dentures which restore the anatomic relationships. A gratifying improvement in general health and a disappearance of many vague symptoms and gastric disturbances may follow.

Figure 30

# cheilosis

## DUE TO LOSS OF VERTICAL DIMENSION

Figure 31

## Case Eleven

Case Twelve

# allergic cheilosis and circumoral dermatitis

A 58 year old white woman developed urticaria following the administration of sulfonamide and other drugs when she had a "cold." From that time on, she became hypersensitive to many things, including various foods such as tomatoes. The lips, circumoral tissues and tongue were particularly affected (figure 32). Large doses of an antihistaminic produced relief (figure 33), but the lesions recurred when it was discontinued (figure 34). Healing followed the administration of a total of 950 mg. of ACTH intramuscularly in divided doses over a period of 10 days (figure 35).

Comment—This patient, who was treated with the antihistaminic and ACTH, then with cortisone and still later with compound F, is now self-supporting, yet these materials have not cured her hypersensitivity. They are given in large doses; then treatment is discontinued. In this way we have avoided continuous treatment and yet have made her life "a happy one."

In such cases we treat only when necessary and integrate specific treatment in the over-all medical care. The practical aspects of administration are adjusted so that they do not interfere with the patient's normal life or work.

Figure 32

Figure 34

Figure 33

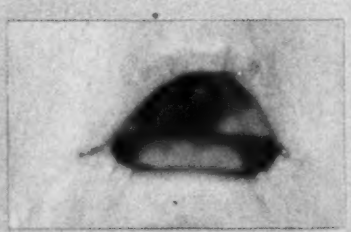


Figure 35

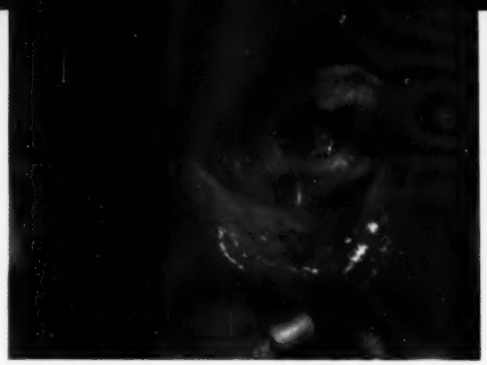


Figure 36

Figure 37

# *allergy* DUE CHIEFLY TO IRISH POTATOES

## Case Thirteen

A 46 year old Negro woman was in perfect health until 1934, when several small blisters appeared on the end of her tongue. She used mouth washes which gave no relief. Then she used borax solution which "almost killed me," and her tongue became so swollen that she could not eat or talk. In the next few years she consulted many physicians and was given many different medications. Frequently her tongue "got in terrible shape," and she could not eat anything or put anything on it until it returned to normal. She noticed that her mouth, tongue and oral mucous membrane became sore when she ate grapes, eggs or milk or used tooth paste. After careful observation for many months we learned that she was especially allergic to Irish potatoes; when she ate a small amount, her tongue became "stiff and cramped at the root" and her mouth became "covered with blisters" which started as small white areas, "opened like a flower" and then became fiery red (figure 36). On these occasions her stomach burned. Diphenhydramine hydrochloride offers relief for this type of symptom. Figure 37 shows her mouth six hours after administering 100 mg. of the drug. In recent years she has avoided foods containing grapes, eggs, milk and potatoes.

Comment—This patient has had her life "made worthwhile" again by the administration of an antihistaminic when she has had reactions, and by avoiding certain foods and other materials which precipitate these attacks.

For more than a decade we have been using antihistaminics in the treatment of many types of allergy. There are some 26 different antihistaminics, and although all are perhaps useful, we have not wished to work with 26 drugs. We use diphenhydramine hydrochloride and tripelennamine hydrochloride and if these are ineffective, we try others. The antihistaminics have many pharmacologic properties. One reason for their use in anaphylactic reactions, severe allergic shock, urticaria, angioneurotic edema and hay fever is their antihistaminic effect. Also, we use diphenhydramine as a sedative and for atropinelike activity. We do not recommend taking antihistaminics and continuing to eat foods which cause an allergic reaction. It is of utmost importance to give adequate doses and to try other antihistaminics when one is ineffective.

Pituitary ACTH, cortisone and compound F frequently are effective in preventing or retarding these hypersensitivity reactions.

Figure 38

# acute cheilosis

## ASSOCIATED WITH RIBOFLAVIN DEFICIENCY

### Case Fourteen

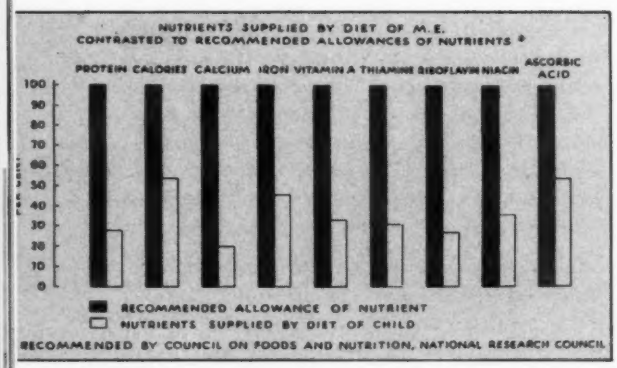



Figure 39

Figure 40

A seven year old white boy of Anglo-Saxon ancestry, whose family we had been studying for many years, developed acute cheilosis (figure 38). He felt weak, had pains in his legs and eyes, was generally irritable, and didn't feel like playing. His diet, which was studied in detail, was deficient in riboflavin as well as other essential nutrients (figure 39). He was treated with riboflavin, and the lesions at the angles of his mouth disappeared. We observed him frequently during the following 10 years and from time to time gave him nutritional supplements, with the result that he has grown into a well-developed young adult.

The foods included in his diet were suitably prepared and fed in the same relative proportion to a group of 50 day old rats, while another group of litter mates of these rats was given an adequate diet. The rat shown at the top of figure 40 received a diet similar to the boy's, and the rat below received an adequate diet; it is clear that the boy's diet was inadequate for the growth and proper development of a young white rat.

Comment—Now that much of the dust raised by discovery of the vitamins is settled, it is possible to see ahead more clearly and to evaluate better the etiology of deficiency diseases. As shown in this case, we now know how to use riboflavin in treatment of cheilosis arising from lack of this substance. Like nicotinamide and ascorbic acid, riboflavin may serve as a hydrogen transporter. In some instances it can reversibly oxidize and reduce, and combined with specific proteins it forms an elaborate enzyme complex. Our clinical studies have suggested that riboflavin deficiency is related to protein intake. There is a tremendous need to prevent lesions such as this boy had as well as to detect early deficiency states.

# *gingivitis and glossitis*

## OF UNDETERMINED ORIGIN

### Case Fifteen

This case is representative of a group in which we have been studying a new method of relieving a persistent type of gingivitis. A 54 year old white woman was referred for treatment of persistent gingivitis and glossitis of two years' duration. Topical and systemic medication ranging from mouth washes to vitamin injections had been ineffective. A gingivectomy performed on the upper left quadrant two months previously as a possible therapeutic procedure had provided no relief. Continuous burning and intermittent bleeding of the interdental papillae and marginal gingivae were intensified by eating solid foods and were frequently so severe that she ate only liquid, bland foods and refrained from brushing her teeth.

Generalized desquamation of the interdental papillae and adjacent gingival mucosa extended for 1 to 2 cm. toward the mucolabial and mucobuccal folds (figure 41). The involved areas were smooth, atrophic, bright red and glistening, and lacked the characteristic stippled appearance. The interdental papillae were blunt and retracted and painful to touch, and oozed blood on slight pressure. The teeth were free of accumulations of subgingival and supragingival calculus. Full mouth roentgenograms contained no evidence of periapical or periodontal pathology. The tongue was slightly irritated at the edges and undersurface. Scattered superficially denuded areas were present on the undersurface of the tongue and in the floor of the mouth.

Laboratory tests showed free hydrochloric acid in the gastric juice, normal peripheral blood findings, and a normal bone marrow. Blood plasma levels of vitamin C, vitamin A and carotene were within normal ranges. Blood chemistry was normal.

Because the lesions developed during the menopause and the chronic inflammatory appearance of the gingivae suggested hormonal dyscrasia, she was given a total of 15 mg. of

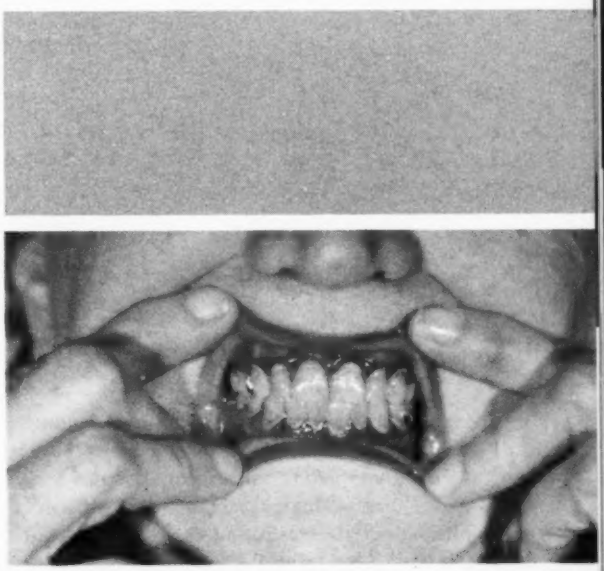


Figure 41

ACTH intramuscularly over a period of 13 days. The gingivae improved noticeably in tone and color, and eating of solid foods and brushing of teeth did not produce pain and bleeding. The lesions did not clear completely, however, and reverted to the pretreatment stage within six weeks following therapy. She was then given mixed vitamins (therapeutic formula) and 15 mg. of folic acid by mouth daily for three months. While some subjective relief was obtained, the gingival lesions remained essentially unchanged. Addition of diphenhydramine hydrochloride every six hours to the vitamin regimen over a two month period provided intermittent freedom from gingival pain and bleeding but failed to alter the character of the lesions. Subsequently she was given compound F in NEO-BASE® ointment (5 mg. compound F in 1 gm. ointment) with instructions to massage the mixture firmly over the involved areas for five minutes every two hours. Figure 42 shows her gums after 20 days of this therapy. She has adhered to this procedure for the past 21 months, during which time the gingival lesions

Figure 42

have slowly receded, and bleeding and pain have been completely eliminated. She states that she is now "completely rehabilitated."

Comment—The fine therapeutic results which followed administration of compound F in this case will prove a broad stimulus for further investigation and treatment. The action is obviously at some fundamental biochemical level. This material should be used in general dental and medical practice for this type of lesion. The most important single aspect of treatment will be proper selection of cases.

# *sensitivity*

## TO ACRYLIC DENTURE BASE MATERIAL

### Case Sixteen

This specific type of sensitivity, although rarely described in scientific literature, is more prevalent than most dentists and physicians realize. A 45 year old white man came to the clinic complaining of a sore mouth, weakness, fatigue, depression and a feeling of being "down and out." He had been in good health until three years previously, when his teeth were extracted. General physical examination was essentially negative except that it revealed evidence of considerable loss of weight. Examination of the oral cavity showed hyperemia of

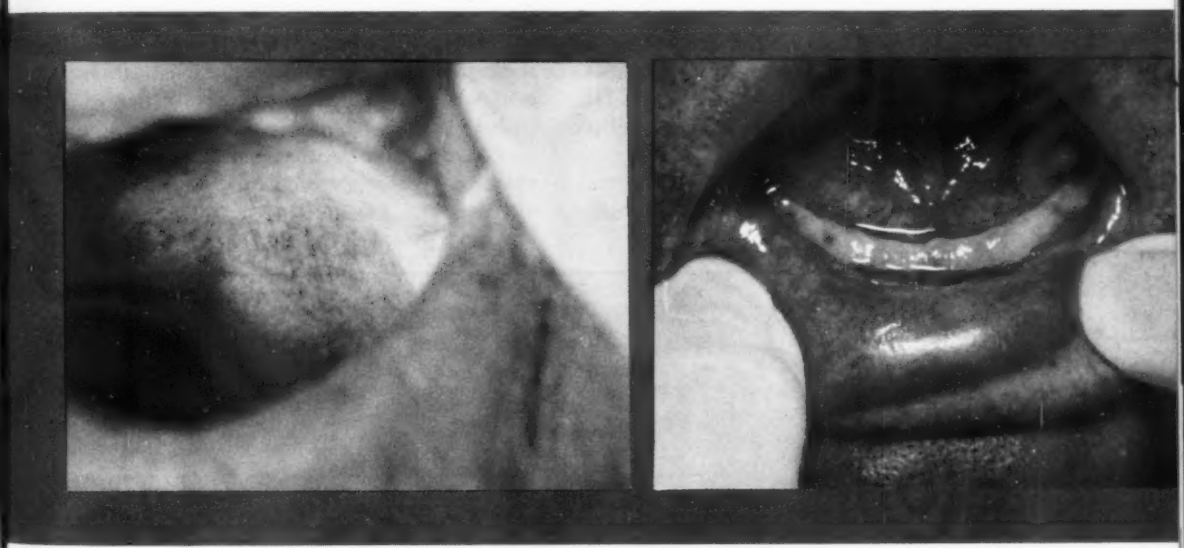


Figure 43



Figure 44

the soft palate (figure 43) and of the buccal mucous membrane. The ridges had a grayish appearance and scattered pigmented spots (figure 44). After he had worn his dentures for three months, the roof of his mouth became swollen and blistered. When he wore the dentures, he noticed that he had increased salivation, a burning sensation of his mouth, and a sore throat.

A skin test to uncured acrylic, which was applied to his forearm, produced a strongly positive reaction on the third day (figure 45), and the reaction remained for three and a half months. Although he was not wearing his dentures when the patch test was made, his mouth became worse. After the reaction subsided, vulcanite dentures were constructed, and these caused no reaction. Since his mouth is no longer sore, his general nutritive state has improved and he is now able to work.

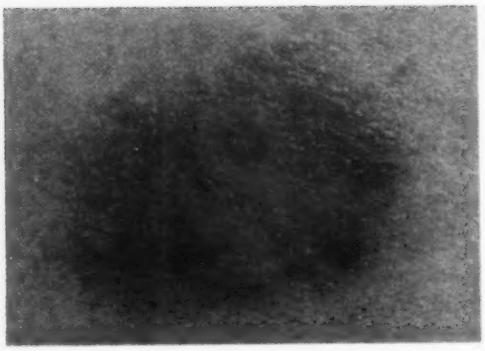


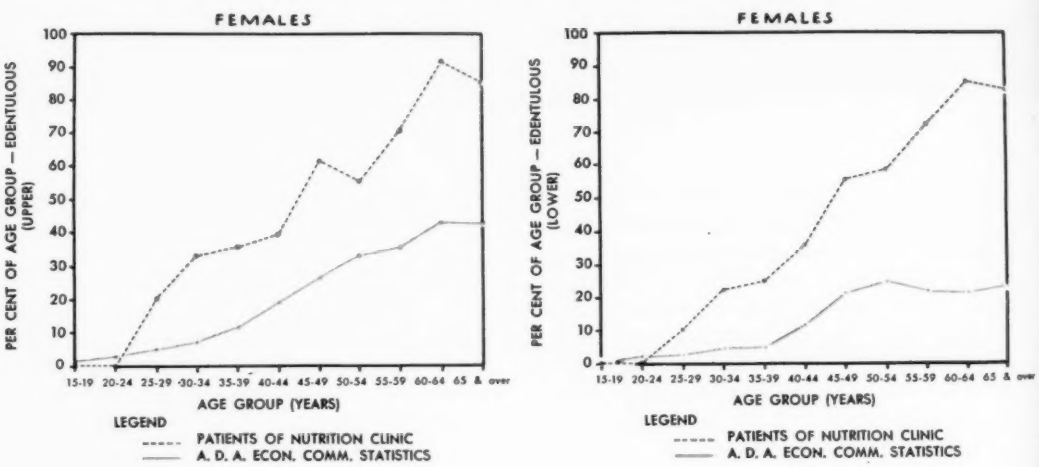
Figure 45

Comment—Acrylic allergy should not be overlooked in the presence of persistent mucous membrane reactions. Dentures constructed from material other than acrylic should be tried when there is no response to routine treatment. In less severe cases the antihistaminics, ACTH, cortisone and compound F are effective palliative agents.

In discussing disease conditions of the oral cavity which arise from nutritional disturbances, we have not as yet mentioned the teeth. We have frequently observed that a high percentage of adult patients who seek relief from nutritional disorders have poor dental function. A relationship between impaired masticatory function and nutritional deficiency diseases has been demonstrated (figure 46). Many persons lose their teeth because of destruction of the supporting tissues following a lack of vitamin C, niacin amide or other nutrients without having the teeth per se adversely affected. It is important to realize that proper mastication is achieved much more easily by natural dentition than by artificial dentures. Poorly constructed and poorly fitting dentures not only impair the masticatory efficiency but also may result in anorexia.

Figure 46

COMPARISON OF THE PERCENTAGES OF FULL UPPER AND FULL LOWER EDENTULOUS PATIENTS IN 7,541 PATIENTS (WALLS, LEWIS AND DOLLAR) WITH THE PERCENTAGES IN 446 CONSECUTIVELY SELECTED PATIENTS OF THE NUTRITION CLINIC



Case Seventeen

## EXTREMELY ABRADED TEETH WITHOUT EVIDENCE OF PAIN

A 70 year old white man came to us because of pain and weakness in his legs, shortness of breath, and tingling in his hands, fingers, feet and toes. A diagnosis of pernicious anemia in relapse was made, and he was successfully treated. His teeth were extremely abraded. The crowns of the lower incisors were worn away. Nothing but roots, the canals of which had been filled in with secondary dentin, remained (figure 47). The posterior teeth were abraded flat. No cusps were present. The pattern of the attrition on the incisors left a "knife edge" at the linguo-occlusal angle, and this sharpness irritated his tongue and had to be rounded frequently.

This man stated that a doctor had given him tobacco as a remedy when he was an infant, and he has been chewing tobacco for as long as he could remember. He probably was chewing tobacco actively by the age of six years.

Comment—It is remarkable that this patient, like many others we have observed, could have such extensive abrasion of the teeth without any pain. Nature protects the vital part of the tooth by depositing secondary dentin against the site of attrition, thus forming a protective cap.

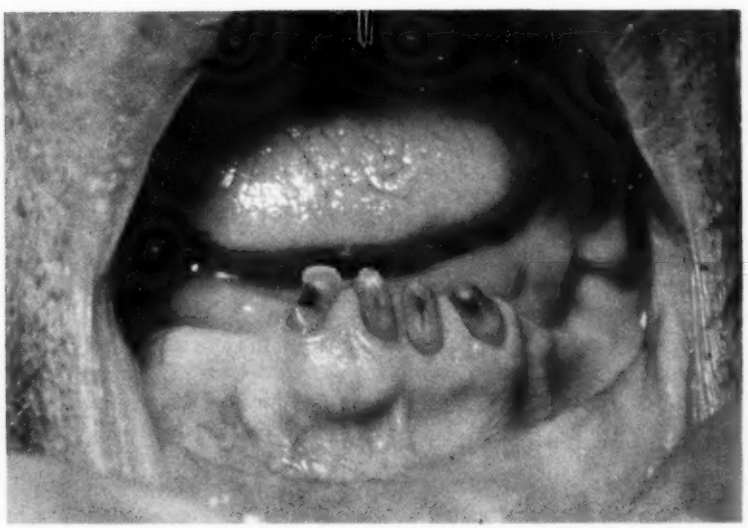


Figure 47

# *dental caries*

## Case Eighteen

This disease is so widespread that it rarely is classified as such by laymen. It can strike at any age. Abundant dietary sugars and carbohydrates and poor dental hygiene can speed up the destruction of the teeth. A six year old white girl was brought to our clinic because of dental caries. Physical examination revealed a well-developed, well-nourished girl. Her history and general physical examination were essentially negative, but it was noted that she ate most generously of cookies and candy each day. The only teeth in this girl's mouth not affected by caries were the two permanent central incisors which had just erupted (figure 48). As can be seen in the tube on the left in figure 49, the saliva from this patient is strongly positive for dental caries activity, compared with that on the right from a person who has no dental caries.

Comment—Irrespective of the age at which dental caries appear, they are associated with yellow discoloration of the involved enamel and dentin. There has been much speculation regarding the mechanism of formation of this yellow color. This pigment has been isolated and identified as a melanoidin. We have produced it in vitro in intact human tooth crowns exposed to the action of a strain of oral *Lactobacillus acidophilus* in a synthetic medium containing glucose. The colors of the artificially produced compound and of the naturally occurring one are identical (figure 50).

From work now in progress we have shown that it is possible for the bacteria of the mouth to build new defenses for themselves. Figure 51 shows the ability to withstand the inhibitory effects of four different antibiotics as "tolerance" is developed in gradually increasing concentrations of these antibiotics.

Before leaving this short discussion of dental caries, we wish to mention some other work now in progress, which from an experimental point of view concerns an effective approach to their control by elimination of fermentable carbohydrates from the diet. This procedure requires *complete* and *absolute* abstinence from desserts, soft drinks, chewing gum, candies and other sugar-containing foods. To assure inhibition by inanition of the sugar-fermenting oral micro-organisms associated with human tooth decay, the diet must be adhered to rigidly for a minimum of six weeks. Because of the sporadic rather than continuous nature of the caries process, all between-meal snacks must be deleted. This diet should be detergent in consistency, i.e., comprised of nonadherent, rough, coarse foods conducive to the frictional cleansing of tooth surfaces. Immediately after each meal a glass of water must be used as a rinse to remove the great bulk of foodstuffs retained in the sheltered areas of the mouth. Brushing the teeth in a manner designed to reach the interdental spaces and necks of the teeth within four minutes following a meal is highly recommended.

Figure 52 shows the change in salivary dental caries activity as measured by our modification of the Fosdick, Hansen and Epple test in one of the persons who followed the aforementioned regimen for six weeks. Each time this rigid restriction of diet is broken, the dental caries activity test again becomes positive; adherence to the monotonous experimental diet again reverses the reaction.

(Nine-alpha fluorodihydrocortisone is even more effective per unit of weight for local application than is compound F itself. It is available to practicing physicians.)

In the next section we shall illustrate and discuss some problems arising within the skin. For the most part, patients such as these are neglected. Frequently they are told that nothing can be done for them, that if they live long enough they may overcome their condition, that they must learn to live with these problems, and that all they need do is make proper adjustments, eat better, or avoid deleterious substances or situations.

Figure 48

Figure 50

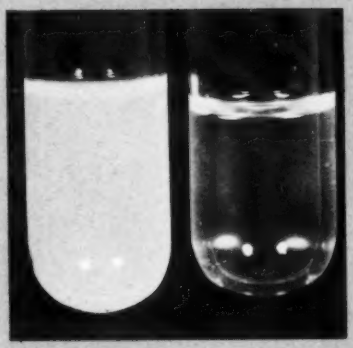


Figure 49

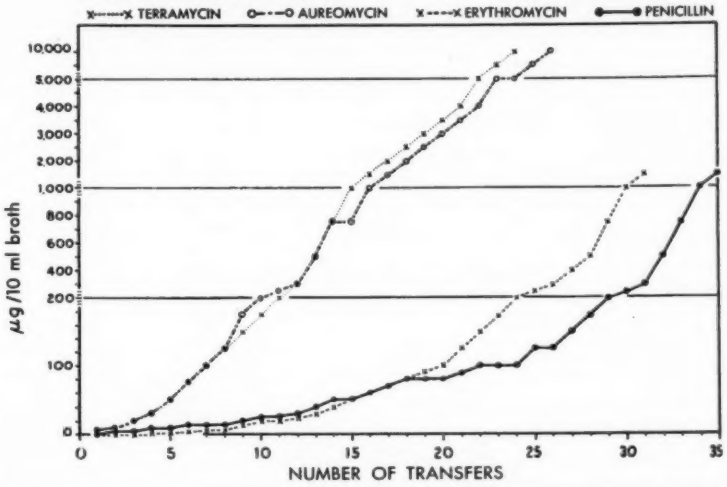



Figure 51

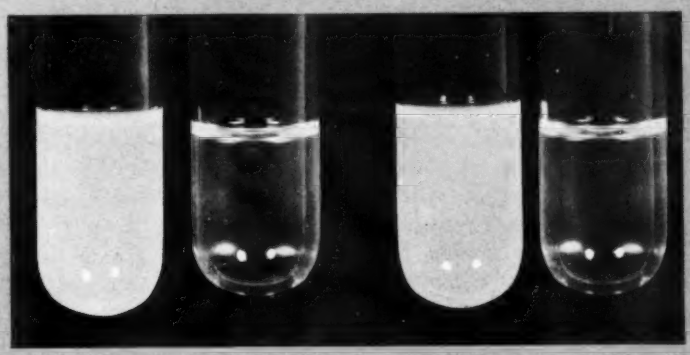


Figure 52

# dietary deficiencies and dermatologic diseases

Literally this is a hungry world. Many larders are pitifully stocked. Because some of us temporarily control our environment, we may mistakenly think there is an abundance of food for all. Yet in many densely populated countries the diet is largely vegetarian and the food supply is inadequate even to satisfy hunger. Food and dietary habits of all human beings are concerned with agriculture, economics, culture, tradition and individual preferences.

All of us consume food—a trivial thought *only* to a man with a full stomach. It is an eternal truth that a human being will seek food for himself and for those he loves, but he may not, and frequently does not, find the proper foods in the proper amounts at the right time. He is interested primarily in satisfying hunger. He does not understand about amino acids, fatty acids, carbohydrates, proteins, vitamins and minerals. He does not understand that one essential nutrient cannot replace another, that if a single nutrient is omitted the diet is deficient, and that all the cells without proper nutrition will not remain passive spectators indefinitely.

In our age of ever-increasing scientific advances and specialization the hard-working practicing physician faces a challenge when a patient with any nutritive or metabolic disorder comes under his care. In many instances laboratory tests aid so little; yet in some instances they are so necessary. Diagnosis must depend on a reliable history and a careful physical examination integrated with any pertinent laboratory findings.

A new era has arrived. Thiamine, ascorbic acid, niacin, riboflavin and folic acid have been most important in bringing many people health. Recently vitamin $B_6$, biotin, pantothenic acid and vitamin $B_{12}$ have been accepted as being essential for man. The essence of treatment is precise diagnosis.

As already pointed out, certain persons are especially prone to have nutritive disorders; yet of the many thousands of individuals we have seen, no two have had identical lesions.

Dermal lesions, often diagnostic of deficiency states, may appear on any part of the body. Textbooks usually show the rare lesions which usually represent the far-advanced diseases. In general, the lesions of deficiency diseases tend to be located over areas of irritation—on the backs of the hands, on the fronts and backs of the wrists, on the elbows, over the face, around the neck, under the breasts, over the knees and feet, and in the perineal region. Lesions are often bilaterally symmetric and separated from the healthier-appearing skin by a very sharp line of demarcation. They are never static and vary greatly from patient to patient. Lesions frequently follow trauma and may be accompanied by burning, itching and pain.

Just as pellagra can exist as a true form in the absence of a rough skin (pellagra sine pellagra), so can there be dermal lesions without glossitis and stomatitis. Likewise, purpuric spots of anemia and scurvy can be present without other clinical manifestations of these syndromes. Since the same methods of treatment relieve the patient, whether or not all tissues present visible lesions, the absence of certain so-called characteristic lesions should never delay the initiation of proper specific therapy.

In the northern part of the United States pellagra nearly always is associated with severe alcoholism or organic disease. Clinicians now

consider what they once diagnosed as pseudopellagra, pseudoalcoholic pellagra or pseudoalcoholic dermatitis to be true pellagra.

Patients with pellagrous dermatitis or other clinical symptoms of pellagra can be relieved by sufficient amounts of therapeutic agents, food, rest and general care. Such patients are advised to stop drinking completely, as all deviations tend to allow recurrences. It should be explained and emphasized that they should never again take alcoholic beverages.

The patient with pellagrous lesions secondary to chronic alcohol addiction will benefit greatly from treatment, because it restores to the body all the elements needed and results in improved health. We give high protein, high caloric diets, and dried brewer's yeast powder and nicotinic acid where indicated. All our patients have responded to therapy and remained well when they stopped drinking and maintained an adequate nutritional status.

It was long thought that pellagra resulted from some poison or intoxication and it once was believed to arise from infections. Our clinical and experimental studies have shown that pellagra is a nutritive disorder, and any disease can predispose to its development. The dictum, "Once a pellagrin, always a pellagrin," once universally accepted, has been relegated to oblivion by application of modern knowledge of nutrition.

Alcoholic pellagra is closely related to endemic pellagra in that inadequate diet plays a role in pathogenesis. The four case reports which follow are examples of pellagra secondary to organic diseases.

# *pellagrous dermatitis*

## SECONDARY TO HYPERTENSIVE HEART DISEASE

### Case Nineteen

A 38 year old white woman came to the clinic complaining of "skin trouble" and "dizziness in the head." There was no history of alcoholism. Six and a half years previously her physician found that she had very high blood pressure and advised her to eat little meat and to lose weight. She followed the diet for five years and noticed a "breaking out" over her left hand and shortly afterward on her right hand. Her physician prescribed yeast and milk, but she was afraid her blood pressure would rise again so did not take them. Dizziness, headaches, vomiting and diarrhea were noted, and loss of strength and weight continued.

Physical examination showed a well-developed but undernourished woman who was

apprehensive and irrational. The dermatitis on the hands and dorsa of the forearms was diagnostic of pellagra (figure 53). She responded well to antipellagra therapy consisting of dried brewer's yeast powder, 2 oz. three times a day mixed in tomato juice, for eight days.

Comment—This case is significant in that pellagra developed secondary to hypertensive heart disease not because the patient was poverty-stricken but because she had been eating the restricted, inadequate diet prescribed, for too long a period of time. We found it possible to keep her in a good state of nutrition without the hypertension disturbing her unduly.

Figure 53

Figure 54

Case Twenty

# pellagra

## SECONDARY TO ANTIOBESITY DIET

A 36 year old white woman was brought to the hospital with a "nervous breakdown." She was in good health until eight months previously when her physician advised her to lose some weight. She could not afford lean meats and fruits. Her diet consisted chiefly of carbohydrates, refined fats and small amounts of proteins. She lost weight rapidly, but after eight months she was extremely nervous and irritable. Dermal lesions diagnostic of pellagrous dermatitis appeared on the anterior aspects of both ankles (figure 54). Response to 100 mg. of nicotinic acid five times a day was prompt, and she was discharged feeling physically and mentally well.

Comment—Obesity is always tragic, and its hazards are terrifying. One of the most pitiful and perhaps unnecessary hazards is in prescribing antiobesity diets with little concept of the severe metabolic disturbances which may result. While no one questions that it is desirable for an obese person to lose weight, so often physicians prescribe a low fat or low sodium diet without considering that the patient has a low income and that such diets usually are relatively expensive. Few physicians pay any attention to the change in disposition, the development of strange new symptoms, or the feeling of depression and irritability which often follow dietary restrictions in the obese.

## Case Twenty-One

A 36 year old Negro woman with tuberculosis was brought to the hospital because of weakness. We could not reconstruct from her vague history the true nature of the onset of many of her symptoms. Apparently her diet always had been satisfactory and her health good until six months previously, when fever and a profound and slowly increasing anorexia and cachexia developed. Her skin lesions were atypical in location (figure 55). She responded

*pellagra*

SECONDARY TO TUBERCULOSIS

Figure 55

to treatment with nicotinic acid and a highly nutritious diet. The fever and cachexia probably contributed to the development of pellagra; such cachexia seals the doom of the pellagrin unless adequate treatment is given.

Comment—Note the well-demarcated lesions in figure 55. Actually, the "normal" skin is normal only to the naked eye. Clinicians have stressed the gross skin changes in disease states rather than the physiologic disturbances. We

Figure 56 *top;* Figure 57 *center;* Figure 58 *bottom*

have pointed out repeatedly that the morphologic changes of the skin are of the same type, whether in the lesion or in apparently normal skin; the difference is one of degree only. Figures 56, 57 and 58 are photomicrographs taken from biopsy specimens of the skin in pellagra. Note particularly the hyperkeratosis and the acanthosis. Edema of the collagen of the cutis is apparent. These microscopic lesions are similar to those found in chronic inflammatory skin diseases. Many photomicrographs of clinically uninvolved areas of skin in pellagra show essentially the same thing, but to a much lesser degree.

Cutaneous lesions often occur simultaneously in different parts of the body in different phases, e.g., a lesion in an early stage on the arm and one in a healing stage on the leg. This brings into sharp focus the importance of local mechanisms superimposed on the background of systemic defects resulting from chemical deficiencies. Many dermal lesions of pellagra, scurvy or the purpura associated with allergies or the anemias are asymmetric, yet since the blood is uniform at a given time, discrepancies among the lesions must result from purely local causes. Dermal pressure, irritation, physical disturbances, friction, local irritants, burns and scars all predispose to a localization of what ultimately is the clinical lesion.

Endemic deficiency diseases occur in either sex of every race, and their clinical pictures are extremely complex with many subnormal and borderline nutritional disorders. The poorly defined, general symptoms include loss of weight and strength, insomnia, depressed mental state, nervousness and irritability, headache, diarrhea, indigestion, abdominal cramps, heartburn and vague paresthesias. When we study a patient with a nutritional disorder, we also study all members of his family who live together and eat similar diets, as well as the pets and domestic animals and fowl. Once a deficiency disease is established, much information can be derived from studying the family as a whole over a period of time.

Case Twenty-Two

# endemic pellagra

## DUE TO INADEQUACY OF NICOTINAMIDE AND TRYPTOPHAN

A 58 year old white man came to the clinic because of painful lesions of the face and neck of six weeks' duration (figure 59). A dietary history showed that for economic reasons he had limited his diet for some time to corn bread and other corn products, rice, coffee and syrup, with vegetables occasionally and a piece of meat (chiefly fat meat) rarely. He lost 50 pounds within a year. He did not imbibe alcohol in any form. The skin lesions subsided following dietary treatment (figure 60), and he was discharged from the hospital two months after admission.

Comment—This man's diet was similar to that of other endemic pellagrins, and on the basis of these studies we devised a "pellagra-producing" diet for animal experimentation. We thought the theory that vitamin G deficiency disease of rats was analogous to pellagra in humans was in error. Accordingly, we chose 24 seven week old albino rats from four litters and divided them into four groups. They were all fed a basal diet of corn meal, pork fat, artificially colored maple syrup, polished rice, cornstarch pudding and sugar. Each constituent was in the same relative proportion as in the diet eaten by pellagrins. All groups were given the basal diet ad libitum. Group 1 received the basal diet only. Various supplements were added daily in groups 2, 3 and 4: (2) 1.5 gm. desiccated hog stomach; (3) 1.5 gm. yeast, and (4) 1.5 gm. casein. Groups receiving stomach tissue and yeast ate larger amounts of the food offered than the animals receiving the basal diet alone (figure 61). Figure 62 shows a representative rat from the group receiving hog stomach, one from the

Figure 59

Figure 60

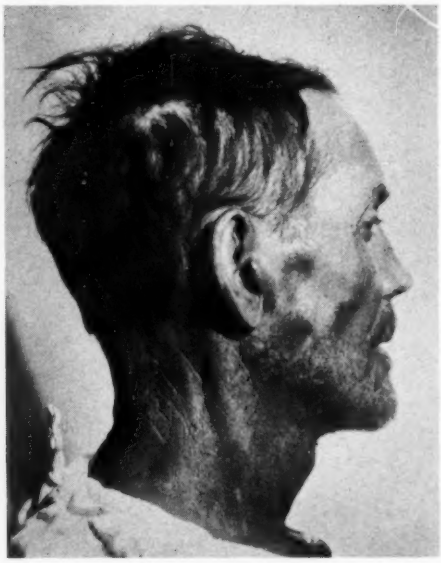


Figure 62

group receiving yeast and one from the group receiving the basal diet only. Priapism, which develops in rats on a deficient diet, was noted in the group on the "pellagra-producing" diet at the end of 40 days (figure 63).

The results of these studies indicate that the diet of the patient in case 22 was not satisfactory for the proper nutrition and maintenance of young white rats and, along with our other studies, demonstrated that "vitamin G deficiency" was not an analogue of human pellagra.

This "pellagra-producing" diet was fed to normal, healthy dogs. Figure 64 shows one of these dogs after several months on this diet. Obviously it was not adequate for proper nutrition of dogs either.

Figure 61

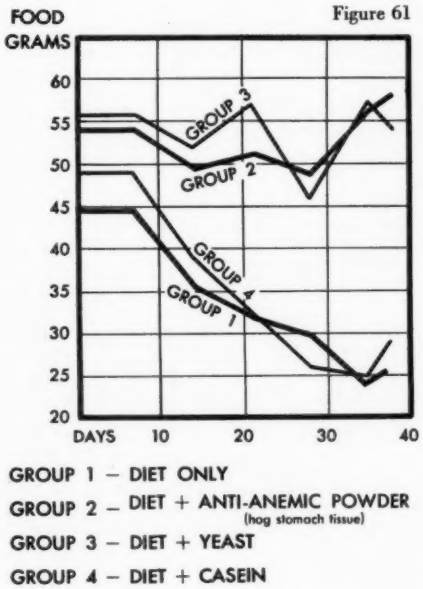



Figure 63

Figure 64

Because so many people were unwilling to accept the probable biologic origin of mixed deficiency diseases, we studied 500 pellagrous patients and devised a representative basic diet from data compiled from their diets. We fed this diet to young white rats, both alone and including certain supplements. The results are shown in figure 65. In this group of 500 patients it is interesting to note that there were many more white than Negro patients (the ratio being more than 9 to 1). Many of the whites were said to live in "pellagra houses" and were sometimes spoken of as "poor white trash." There was a much higher incidence among women, and this can be explained on the basis of failure of the poor diet to supply the increased need for nutrients during pregnancy and lactation.

Figures 66 through 71, chosen from these 500 cases, show pellagra dermatitis varying from acute bullous lesions over the hands to chronic dermal changes.

A physician cannot study a very ill pellagrin without observing his generally disturbed metabolism. Altered fluid and electrolyte balance frequently results because he often refuses to eat food or take fluids. Nausea, vomiting and diarrhea are common symptoms. A diet low in proteins and vitamin $B_1$, eaten over a long period of time, is likely to cause disturbance of osmotic concentration and perhaps of cardiovascular function. Pitting edema is common, indicating excess fluid locally.

The area affected by dermal lesions of pellagra is at first likely to be erythematous and to "itch terribly"; later it becomes swollen, tense and often fiery red. Still later the color becomes reddish-brown and desquamation begins (always in the center and not around the borders). The underlying skin may become abnormally thickened and permanently pigmented, or it may become atrophied.

After we had established that the peripheral neuritis of pellagrins was beriberi due to lack of vitamin $B_1$, we treated many patients who had a mixture of beriberi and pellagra.

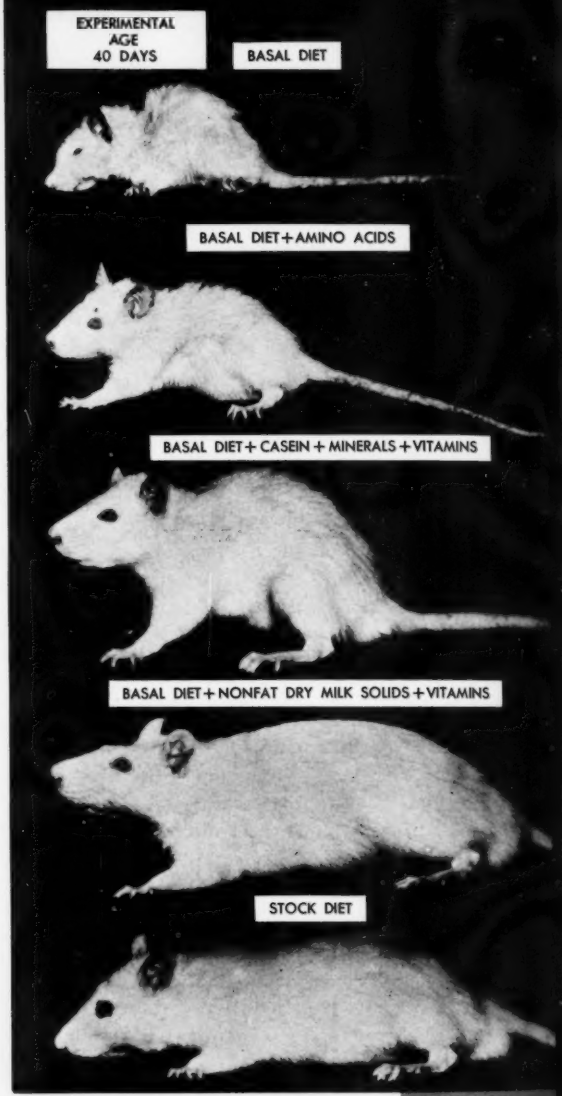

EXPERIMENTAL AGE 40 DAYS
BASAL DIET
BASAL DIET + AMINO ACIDS
BASAL DIET + CASEIN + MINERALS + VITAMINS
BASAL DIET + NONFAT DRY MILK SOLIDS + VITAMINS
STOCK DIET

Figure 65

Figure 66

Figure 67

Figure 68

Figure 69

Figure 70

Figure 71

Case Twenty-Three

# endemic scurvy and pitting edema

A widower of undetermined age came to us because of fatigue and weakness and "bruises" on his skin which had been present for some years. Recently he had noticed bruises related to slight trauma. His legs were weak, and the knee joints painful and swollen. Several weeks before we saw him, purpuric areas developed on the legs (figure 72). His ankles became swollen when he walked. He had been told by a physician that he had "heart disease and dropsy." This man cooked his own meals and occasionally ate alone in restaurants; he had not eaten vegetables, citrus fruits or tomatoes for many months. He had considerable anemia; his red blood cell count was 3.10 million and his hemoglobin 70 per cent. Plasma proteins were somewhat low. His temperature was 101° F. He was given 500 mg. of ascorbic acid orally daily, and within three weeks he was greatly improved.

Comment—This patient was bordering on vascular collapse when we first saw him. He had multiple deficiency diseases, but the response to vitamin C indicates that lack of this vitamin probably exceeded that of other essential nutrients. It is well known that most older patients who have scurvy are widowers or bachelors, who seem unable to live alone and still create a satisfactory home for themselves. They tend to eat irregularly, and often eat inadequate amounts of vegetables and citrus fruits.

Figure 72

The pathogenesis of the various nutritional anemias is so little understood at this time that we cannot hope to grasp precisely the interrelationship between the various altered biochemical substances operating simultaneously within the body of the affected person. What we term the chemical era in treatment of macrocytic anemia has thrown some light on how these related groups overlap. It is understood that persons with macrocytic anemia and megaloblastic arrest who respond to folic acid, thymine, folinic acid, vitamin $B_{12}$ or other substances which act similarly often have an accompanying pitting edema. Such a case follows:

Case Twenty-Four

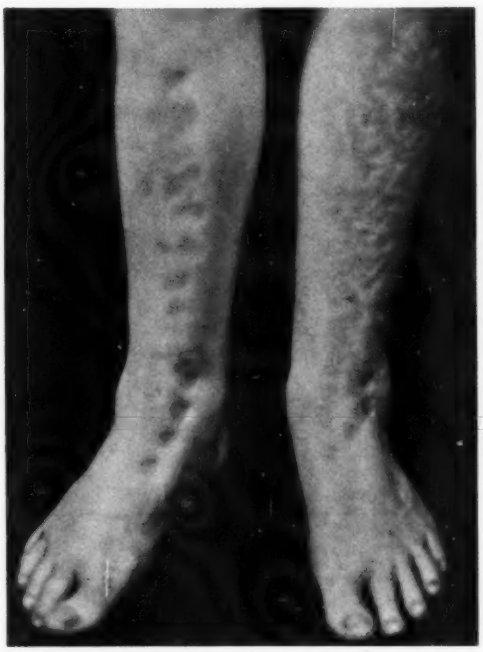
# *pitting edema*

## ASSOCIATED WITH NUTRITIONAL MACROCYTIC ANEMIA

A 38 year old man with nutritional macrocytic anemia had eaten a diet deficient in animal proteins for many years. Weakness, shortness of breath, swelling of the ankles, soreness of the mouth and "heaviness" of the lower extremities developed insidiously, beginning 18 months previously. He continued to work until two days before his admission when he became dizzy. He lost weight despite the fact that his ankles were swollen (figure 73). Gastric analysis showed free hydrochloric acid. The red blood cell count was 2.1 million and the color index was 1.4. The bone marrow was hyperplastic and showed megaloblastic arrest. Pitting edema of the ankles and legs had been present for some time and increased when he walked. He responded well to 10 mg. of folic acid given orally daily for 30 days. The edema disappeared and his blood values returned to normal levels. Two months after admission, he returned to his work.

Comment—Many patients with pernicious anemia, nutritional macrocytic anemia and sprue have no edema on admission, but it develops after blood regeneration and clinical improvement are initiated, disappearing gradually without any change in treatment. The pathogenesis of this is not clear. At times this type of edema is superimposed on true cardiovascular disease. Some benefit results from removing the deficiency state, but the underlying cause such as arteriosclerosis or heart disease is not relieved. The physician may so restrict the patient's diet that he induces edema.

Figure 73



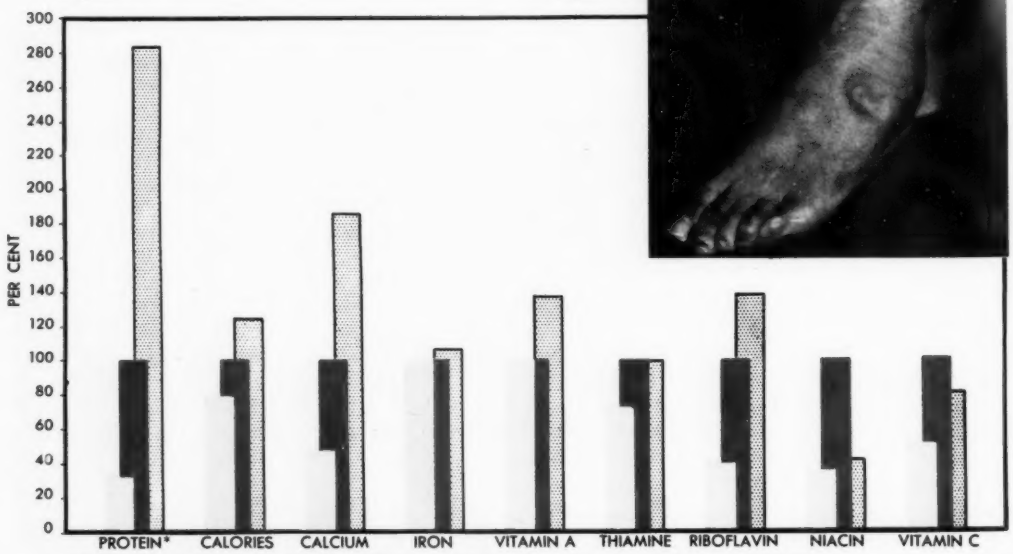
Case Twenty-Five

## CHRONIC WASTING WITH

# *hypoproteinemia and edema*

Figure 75

Figure 74




*BEFORE THE ADDITION OF THE PROTEIN SUPPLEMENT ALL THE PROTEIN IN THE DIET WAS FROM VEGETABLE SOURCES. WITH THE ADDITION OF THE PROTEIN SUPPLEMENT 15% OF THE PROTEIN IN THE DIET WAS FROM VEGETABLE SOURCES AND 85% WAS FROM ANIMAL SOURCES.

NUTRIENTS SUPPLIED BY DIET BEFORE THERAPY.
ALLOWANCES OF NUTRIENTS RECOMMENDED BY COUNCIL ON FOOD AND NUTRITION, NATIONAL RESEARCH COUNCIL.
NUTRIENTS SUPPLIED BY DIET AND PROTEIN SUPPLEMENT.

A 66 year old retired school teacher complained of weakness and diarrhea of five years' duration. For a number of years his appetite was poor, and he lost weight and strength. For 18 months he ate only small amounts of vegetables, corn meal, bread, sugar and coffee. His diet before treatment supplied only about one-third of the recommended allowance of protein (figure 74). He was short of breath and could not walk or stand. There was pitting edema of the ankles (figure 75). Because of severe protein deficiency, he was given a special protein supplement made from milk. It was given in a liter of whole milk, so that he received 175 gm. of protein and 1300 calories from this mixture alone. Note in figure 74 the increase in protein intake with the protein supplement. Within 10 days he lost 20 pounds and had no clinical evidence of edema. Although he appeared much more emaciated than before treatment, this was due to loss of water. Within five weeks the plasma protein levels increased from a total of 3.9 gm. per cent to 5.2 gm. per cent. The albumin increased from 2.2 gm. per cent to 3.6 gm. per cent. He returned to work, and at present (four years later) is well.

Comment—Many persons eat little or no animal protein, and some of them develop low plasma protein levels and clinical edema. When the plasma protein is sufficiently low, as in this case, anemia also may develop and should be treated. We strongly recommend high protein diets in treating the vitamin B group of deficiency diseases.

Laennec's cirrhosis or alcoholic cirrhosis is by far the most common liver disease in the United States. Undoubtedly there are many predisposing and precipitating factors, but it is highly probable that the changes are of nutritional origin. Sufficiently restricted diets can result in full-blown and fatal cirrhosis in infants and children. Early cases are greatly improved by dietary treatment. In animal experiments the absence of the labile methyl group results in cirrhosis. Undoubtedly, in some parts of the world many adults with Laennec's cirrhosis have not used alcohol, yet there does seem to be some association with alcoholism. The typical case gradually has replacement of the liver tissue first by fat and later by connective tissue. The regenerative power of the liver is striking, and the physician must explain to his patient that the "poisoning" must cease and that proper dietary supplements are necessary for producing new liver cells.

A 31 year old Negro woman was brought to the hospital complaining of "dancing lights before my eyes" and poor night vision of one year's duration. Physical examination showed a small, somewhat undernourished woman with generally rough skin, which showed follicular hyperkeratosis (figure 76). Using Kimble's method we found 92 µg. per cent of vitamin A in the plasma. Vitamin A, 300,000 I.U. daily, was administered for two weeks. The vitamin A level promptly increased, the abnormal eye symptoms disappeared and the skin gradually became soft.

Comment—Although vitamin A is best used prophylactically, the specific syndrome of vitamin A deficiency can be relieved promptly with vitamin A in the form of carotene in oil, cod liver oil or potent fish liver oils. Synthetic vitamin A also is available. When administered in too large amounts over too long a period, vitamin A is toxic; this was first revealed when severe intoxication developed among arctic explorers who ate large amounts of polar bear liver, one of the richest sources of vitamin A. Some preparations now on the market contain too much for long-continued daily administration.

Figure 76

# NUTRITIVE FAILURE AND HYPOTENSION

A number of medical investigators have written about the association of skin diseases and deficiency states. There is much idle speculation on their possible relationship to such diseases as acne, psoriasis, urticaria, vitiligo and achylia gastrica. Pallor of the skin often is considered significant in indicating the presence of anemia, and often our patients tell us their neighbors have commented on their pallor and suggested they might have "anemia." We will discuss this further in another section.

While studying nutritive failure, we noted that most patients had blood pressure determinations below normal, and these tended to rise slightly as we corrected the nutritive failure. Since we were studying DOCA® (desoxycorticosterone acetate) and its effect on blood pressure and sodium retention, we selected three patients who had been under observation for a number of years and studied the effect of DOCA on their low blood pressures. A representative case follows:

## Case Twenty-Seven

A 40 year old white woman came to the hospital complaining of weakness and vertigo. She was underdeveloped and undernourished and appeared tired and ill. When we administered sterile water or sterile saline, her blood pressure did not increase, but the injection of 105 mg. of DOCA in six days resulted in an increase in weight and blood pressure (figure 77). Also, pitting edema developed (figure 78). When administration of DOCA was discontinued, the blood pressure readings promptly returned to normal, as did the body weight, and the edema disappeared.

Comment—Water and electrolytes constitute an integral part of all living tissues. Administration of some of the hormones of the adrenal cortex causes retention of sodium, accompanied by retention of water by the kidneys, with the result that edema develops and body weight is increased. There is also a striking increase in blood pressure and body weight such as occurs following daily injections of

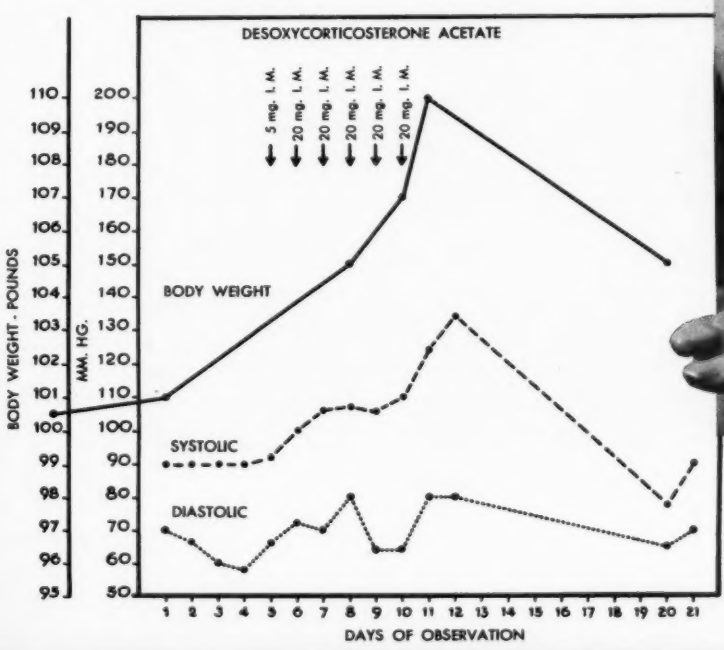



Figure 77

Figure 78

desoxycorticosterone acetate (figure 77).

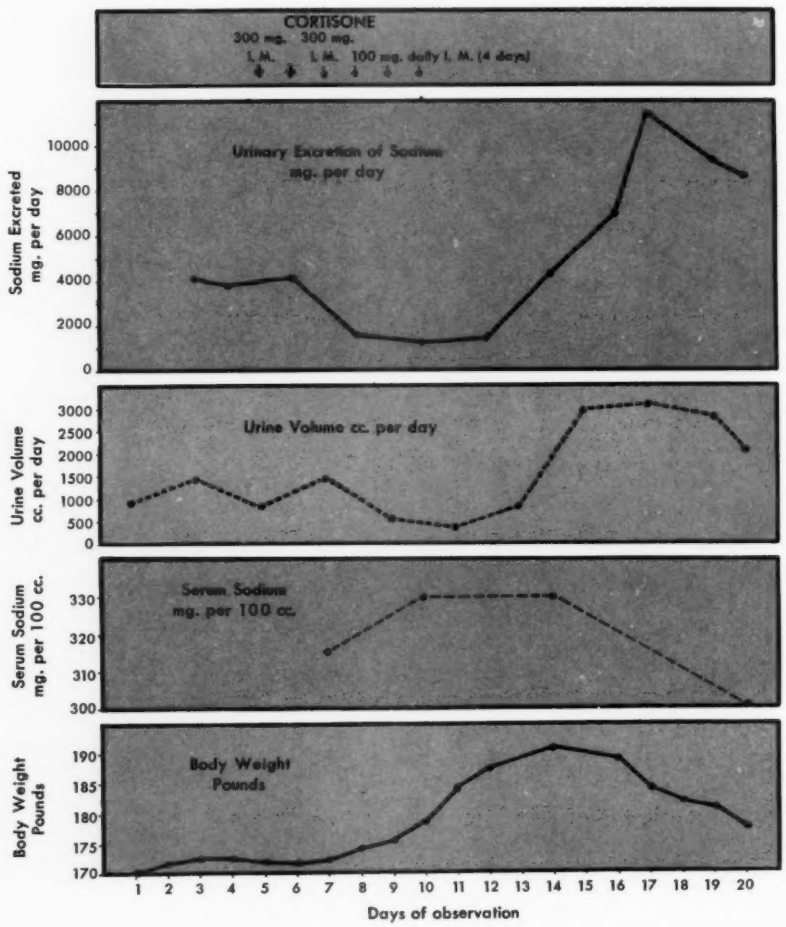
Cortical steroids are necessary for metabolic reactions, and we think these reactions are determined primarily by the needs of the tissues. An up-to-date nutrition or metabolic clinic must have available a highly trained person to determine on short notice the electrolytes in the tissues and fluids as indicated. We are fortunate in having William Niedermeier and Henry Spies. The five illustrations which follow are from Niedermeier's data.

Since there has been some confusion at times concerning the units of measurement which we speak of as milliequivalents, we are using in the illustrations milligrams per cent. Their special usefulness is in the estimation of the electrolytes of the plasma, which is becoming a commonplace laboratory procedure.

One of the most interesting metabolic effects of the cortical steroids is their role in regulation of sodium and potassium metabolism. Figure 79 shows the effect of large amounts of cortisone on sodium metabolism in a patient with rheumatoid arthritis. The degree of sodium reten-

Figure 79

EFFECT OF CORTISONE ON SOME FACTORS OF ELECTROLYTE METABOLISM OF A PATIENT (W. A.) WITH RHEUMATOID ARTHRITIS.



tion is indicated by the marked decrease in urinary excretion of this ion. A decrease in urine volume occurred simultaneously with an increase in the serum sodium concentration. Retention of large amounts of sodium and water results in formation of pitting edema, the degree of which is indicated by the increase in body weight during therapy.

DOCA (desoxycorticosterone acetate), another of the adrenocortical steroid hormones, has no therapeutic value in rheumatoid arthritis but is some 10 to 20 times more active than cortisone in causing retention of sodium. Figure 80 shows the effect of DOCA on the electrolyte pattern of a patient with rheumatoid arthritis. Sodium ascorbate was administered simultaneously with DOCA in an unsuccessful effort to alleviate the arthritic symptoms. The sodium ascorbate

EFFECT OF DOCA ON ELECTROLYTE PATTERN OF A PATIENT ON HIS USUAL DIET.

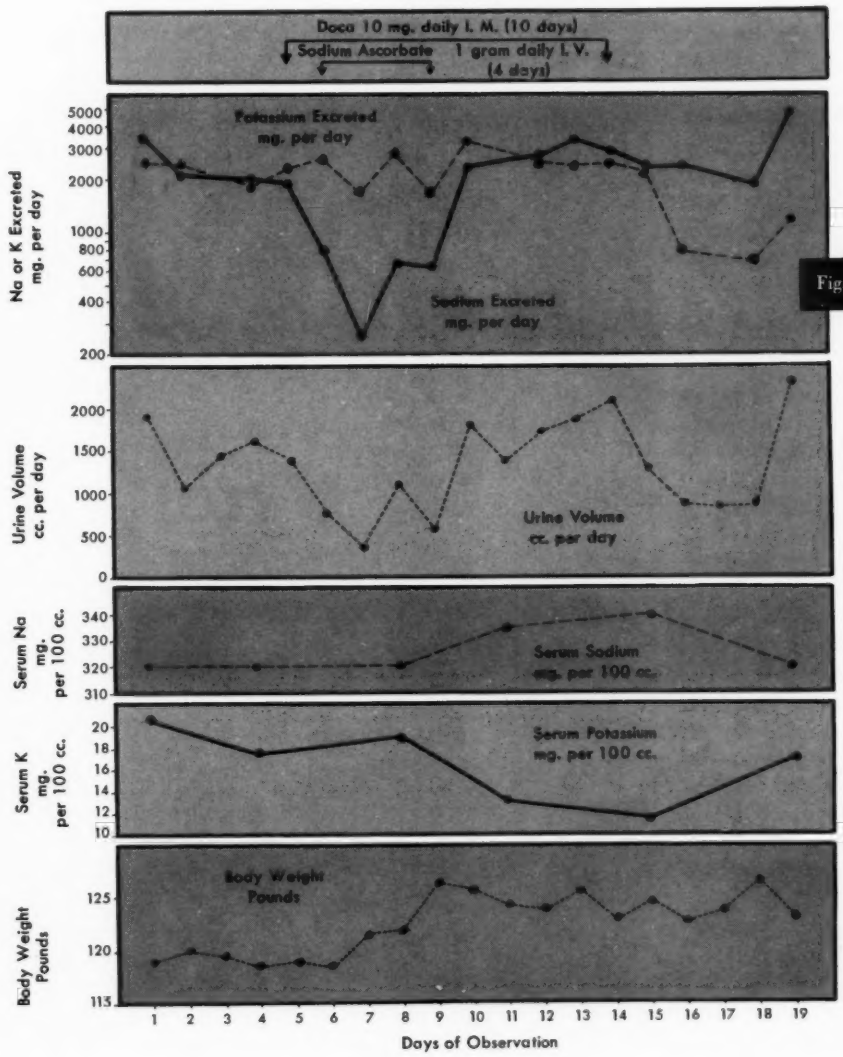

Doca 10 mg. daily I. M. (10 days)
Sodium Ascorbate
1 gram daily I. V. (4 days)
Na or K Excreted mg. per day
Potassium Excreted mg. per day
Sodium Excreted mg. per day
Urine Volume cc. per day
Urine Volume cc. per day
Serum Na mg. per 100 cc.
Serum Sodium mg. per 100 cc.
Serum K mg. per 100 cc.
Serum Potassium mg. per 100 cc.
Body Weight Pounds
Body Weight Pounds
Days of Observation

Figure 80

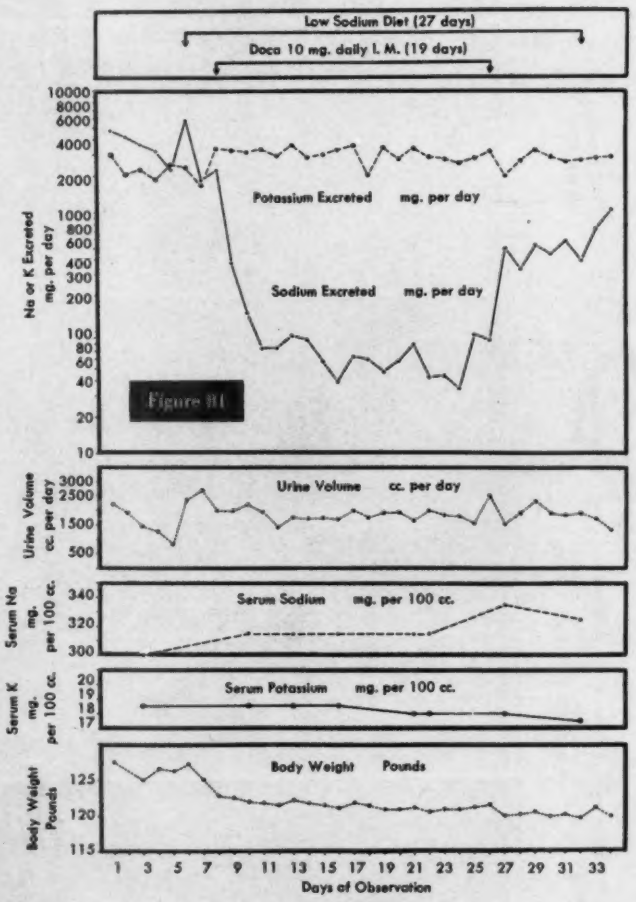
had no measurable effect on electrolyte metabolism. Only 10 mg. of DOCA daily caused a striking decrease in sodium excretion and urine volume, with an increase in serum sodium concentration and the formation of edema as reflected by increase in body weight. In addition, urinary excretion of potassium increased, followed by a marked decrease in serum potassium concentration.

Occasionally the degree of edema or the decrease in serum potassium concentration becomes so great that it is necessary to discontinue treatment. Therefore, we undertook studies to determine methods of preventing these changes in electrolyte balance. Figure 81 shows the effectiveness of a low sodium diet in this respect, and also in preventing the formation of edema in a patient receiving 10 mg. of DOCA daily. The diet is equally effective in preventing the accumulation of fluids due to treatment with large doses of some of the other cortical hormones.

The diet consists essentially of a wide variety of fresh fruits and vegetables, LONALAC®* (a low sodium milk powder), one 2 oz. serving of meat and one egg daily. The marked restriction of the diet as we use it is not very satisfactory to the patient and many will not stay on it indefinitely.

The action of adrenocortical hormones on electrolyte metabolism is not confined to the effect on renal excretion; they probably affect directly all the body fluids and tissues. Figure 82 shows the resultant decrease in the sodium-potassium ratio of saliva when crude pit. ACTH was administered daily to a patient with nonspecific complaints. This ratio reflects the activity of adrenocortical function so accurately that it has been suggested as a diagnostic tool in evaluating adrenocortical activity.

EFFECT OF DOCA ON ELECTROLYTE PATTERN OF A PATIENT ON LOW SODIUM DIET.


Low Sodium Diet (27 days)
Doca 10 mg. daily I. M. (19 days)
Na or K Excreted mg. per day
Potassium Excreted mg. per day
Sodium Excreted mg. per day
Figure 81
Urine Volume cc. per day
Urine Volume cc. per day
Serum Na mg. per 100 cc.
Serum Sodium mg. per 100 cc.
Serum K mg. per 100 cc.
Serum Potassium mg. per 100 cc.
Body Weight Pounds
Body Weight Pounds
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33
Days of Observation

*Supplied by Mead Johnson & Company.

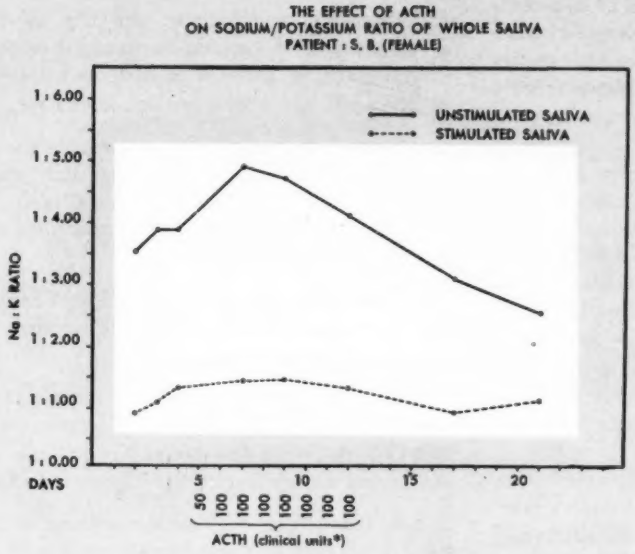



Figure 82

*When ACTH first became available, it was much cruder than it is at present. At that time the only way of measuring it was by weight; hence, milligrams or Armour units were used and, later, clinical units. Soon there will be U.S.P. units. The physician needs to know about clinical units, and when U.S.P. units come out, he will have to know how much is represented in terms of clinical units by one U.S.P. unit. The U.S.P. unit itself will be determined by subcutaneous assay, and it is almost certain that the highly purified material eventually will be defined in terms of U.S.P. units.

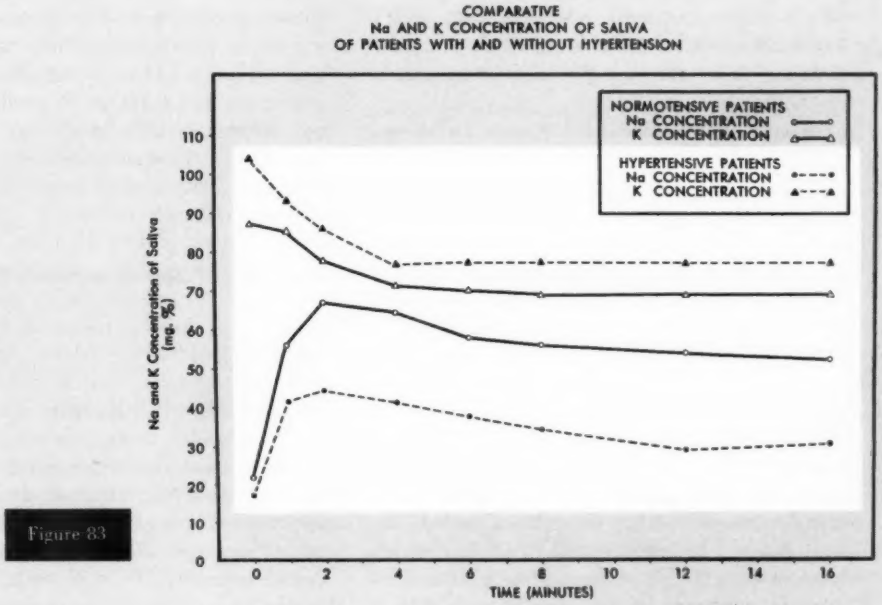



Figure 83

Since the function of the adrenal glands apparently is involved in some cases of hypertension, we undertook a study to determine whether any alteration in salivary sodium and potassium concentrations occurs in such patients. Figure 83 contrasts these salivary concentrations of 27 normotensive persons with 28 hypertensive patients. Since preliminary studies indicated that the sodium and potassium concentrations vary during the period of stimulation (by chewing paraffin), the stimulated saliva samples were collected at various intervals during a 16 minute period of continuous stimulation. Unstimulated saliva is indicated at zero time. As a group the hypertensive patients had a significantly lower salivary sodium concentration than the normotensive group. The difference in potassium was not significant.

Let us return to the therapeutic application of certain hormones. Since 1948 we have been attempting to bring order to the indications and contraindications in the use of ACTH, cortisone and compound F* for the purpose of obtaining maximum benefits. We have learned that there should be no fixed plan of dosage and no rigid prescription as to the time of administration. The authors frequently give pituitary ACTH simultaneously with either cortisone or compound F. We have seen the following mistakes made in therapy with these hormones:

1. Improper selection of patients. In this group are those for whom hormonal therapy is contraindicated, those with little or no active arthritis and those who are uncooperative.

2. Improper dosage. Doses have been too large or too small, given as single daily doses instead of divided, or reduced too rapidly. In other words, the patient's individual need and tolerance were not analyzed.

3. Inadequate supervision. Sufficient clinical and laboratory observations must be made to reveal early signs of overdosage.

4. Neglect of supplementary measures of treatment. The skillful use of salicylates, treatment of coexisting diseases and complications, and proper dietary therapy are important factors.

5. Discontinuance of administration at the time of surgery or during other periods of increased stress.

It is a pity that many physicians are so apprehensive that they do not offer their patients the anti-inflammatory and antiallergic benefits these materials could give. The hormone seems to go a little further in lotion form than in the ointment. Fluoro-hydrocortisone is a very potent derivative and much more potent than the parent substance with the result that in these lotions and ointments, smaller amounts of this compound per unit of weight are required for the same effect.

*Hydrocortisone (compound F) is available for oral use and parenteral administration and is sold under the following names: Merck & Company, Inc., HYDROCORTONE®; The Upjohn Company, CORTEF®; Chas. Pfizer & Co., Inc., CORTRIL®. Ointment forms containing up to 2.5 per cent hydrocortisone are available for topical use.

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Frequently, symptoms arising from the skin reflect systemic disease and aid in an early diagnosis of the basic disorder. Even when there is no visible dermatitis, intractable pruritus on many occasions brings the patient with Hodgkin's disease, lymphosarcoma or other lymphoblastomas to the physician. This pruritus may precede a grossly visible skin eruption by a considerable period of time, and careful microscopic study of the skin may bring to view typical cells. Mycosis fungoides is frequently associated with changes in the lungs. General physical examination, careful history-taking and complete laboratory study including bone marrow and peripheral blood often lead to an early diagnosis of the underlying disorder. In some instances these disorders can be suppressed for a time by the administration of pituitary ACTH, cortisone or compound F. The following case is of considerable interest:

## Case Twenty-Eight

# "Lymphosarcoma"

A 53 year old white woman came to us because of swelling in the neck, "knots" under the arms, "breaking out" of the skin, loss of appetite, weight and strength, and "nervousness." She had a history of "inflammatory rheumatism," but her health had been generally good until two years prior to her admission when she became very fatigued. Her first symptom, a generalized itching of the skin which was persistent and gnawing and made her nervous, was followed in three months by a rash which was most pronounced under her arms and over her chest. Soon thereafter she noted knots in her axillae and neck. Her white blood cell count at this time was 78,000, and a biopsy of a cervical lymph node gave evidence of "lymphosarcoma." X-ray treatments were not effective, and within six months she had lost 20 pounds and was unable to do her housework.

General physical examination showed a well-developed, pale woman with dyspnea. The lymph nodes in the axillae and neck were enlarged and the spleen was palpable. Peripheral blood findings in the bone marrow were consistent with those of lymphatic leukemia associated with a severe anemia. Her hemoglobin varied from 28 to 33 per cent. She was given 25 clinical units of ACTH intramuscularly twice a day for 18 days. During this period she volunteered that she felt better, her strength increased, her nervousness disappeared and the itching of her skin stopped. Within a month she was able to do her own housework. Her appetite increased and she began to gain weight. Her anemia gradually disappeared. At present, two and a half years later, the lymphatic leukemia is still evident from the findings in the peripheral blood and in the bone marrow, but she is free of symptoms. The spleen and lymph nodes are no longer palpable, though the blood contains "leukemic" cells (of course, this patient had both lymphosarcoma and leukemia).

Comment—It is evident that the skin disease was merely a local manifestation of a general disorder. Administration of ACTH increased the steroid level of the plasma and she improved dramatically. However, no one would think that a cure has been effected. She was tided over a critical period, and perhaps her life was even saved temporarily. We do not administer ACTH, cortisone or compound F to a patient when he first walks into our clinic. A complete physical examination must be made prior to therapy. However, in cases such as severe serum sickness, severe drug reactions, severe exfoliative dermatitis or severe bronchial asthma, where death seems imminent, the patients promptly get these materials.

Pituitary ACTH, cortisone and compound F have been of great value to patients in the late

stages of lymphoblastomas; these hormones frequently can take the place, at least in part, of morphine or codeine.

(We have had extensive experience in treating persons with myxedema with either thyroid extract or thyroxin. Some of our patients who had had heart involvement had been treated with digitalis but not with thyroid extract. We also frequently have seen patients with cardiac disease who should have had digitalis but were treated with thyroid extract.)

The thyroid, like so many other glands, may overproduce. The following case is representative of severe hyperthyroidism.

# *hyperthyroidism*

## Case Twenty-Nine

A 27 year old Negro woman was brought to the hospital complaining of "swimming in the head, nervousness and jumping of the heart." For more than a year she was unable to stand noises or get along with her family. She "went to pieces" easily, cried almost constantly, wanted to kill herself, was unable to sleep, and was so warm on even the coldest night that she could not use bedclothes. She lost 45 pounds in a year. Her doctor thought she had high blood pressure and "kidney trouble," but when she did not improve she stopped going to him. Some months later she noticed "popping of the eyes." From the photograph in figure 84 it can be seen that her thyroid was enlarged and she had exophthalmos.

Physical examination showed a well-developed woman with obvious acute hyperthyroidism. Her blood pressure was 130/80 and her pulse 128 or above. Her basal metabolic reading was about plus 90 per cent. A surgical consultant was called, and she was given two 50 mg. tablets of propylthiouracil three times a day and 10 drops of Lugol's solution twice a day. Four months later she felt completely normal; her only remaining symptoms were exophthalmos and the thyroid enlargement. She was in excellent condition for surgery.

Comment—Nutritional and metabolic demands are greatly increased in hyperthyroidism, and most patients do what they can to satisfy their voracious appetites if they can get the food. This, in part, helps to maintain body weight and chemical balance. This case helps to support our working concept that health is

Figure 84

the accurate, harmonious and constant integration of all the necessary biochemical factors in the body. While the primary disturbance was of

endocrine balance, the vitamin balance, electrolyte balance, control of the body temperature and the supply of oxygen to the cells were affected and the harmony of the cells was disturbed. Disturbance of mental processes and physiologic phenomena associated with emotion were noted. We cannot discuss all the many syndromes in this group, but it is gratifying to see the secondary disturbances disappear when the primary condition is relieved.

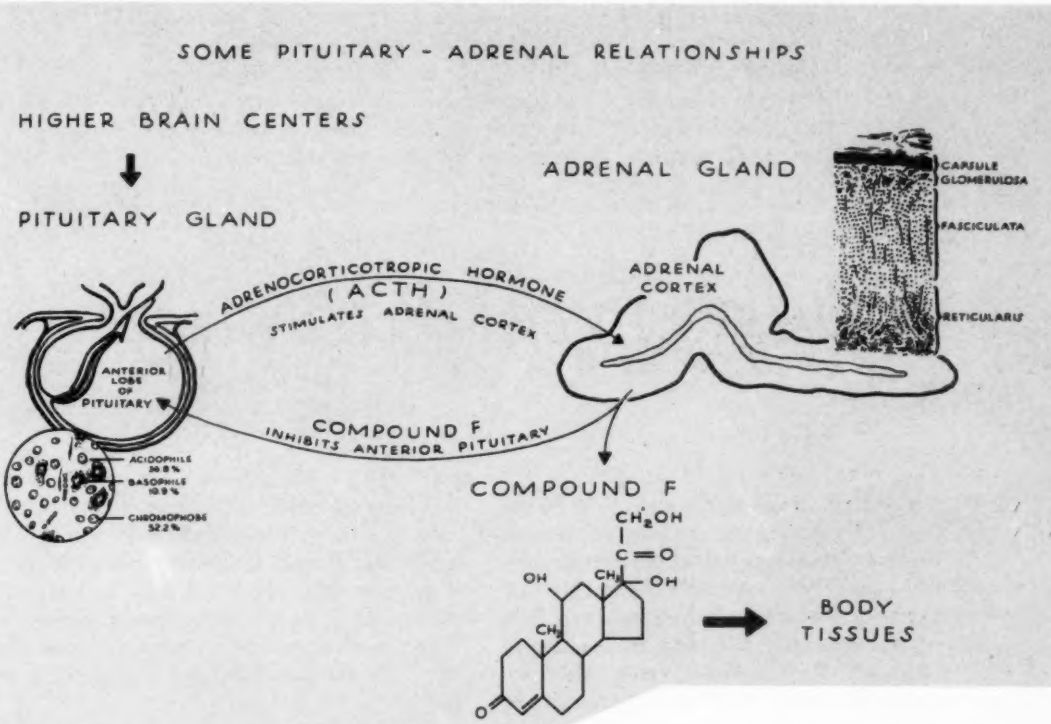
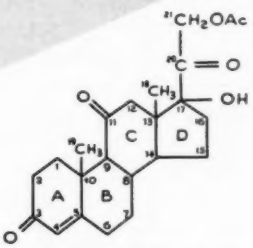


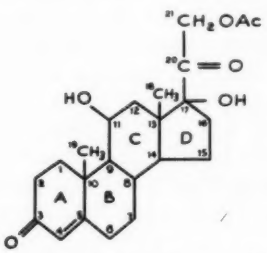

Figure 85



CORTISONE ACETATE

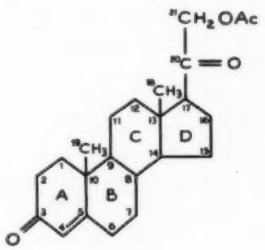
11 - DEHYDRO - 17 - HYDROXYCORTICOSTERONE - 21 - ACETATE

Figure 86



COMPOUND F ACETATE

17 - HYDROXYCORTICOSTERONE - 21 - ACETATE



DOCA

DESOXYCORTICOSTERONE ACETATE

Before discussing the collagen diseases and some of the allergies, we wish to point out the pituitary-adrenal relationships shown in figure 85. Figure 86 shows the chemical formulas of compound F, DOCA and cortisone, which we will discuss further.

Patients with skin diseases repeatedly ask if ACTH, cortisone or compound F might be useful, and we find that their physicians referred them to us to determine this. The practicing physician should use these materials. We have patients with disseminated lupus erythematosus who have survived for several years as useful members of society; although the disease remains, it can be somewhat controlled, as illustrated in the following case:

# *lupus erythematosus*

## Case Thirty

An 18 year old girl was brought to us by her uncle, a physician, from whom we obtained the history. Her illness began four months previously with loss of appetite and strength and with pain in the joints of the hands and feet. About a month later her temperature rose to 103° and 104° F. each afternoon, and after two months a small area of erythema appeared over both malar regions. Four weeks later the lesions became scaly and spread over the bridge of her nose, and numerous small lesions appeared on her neck. A month later she was treated with penicillin and had a severe allergic reaction; the tongue and oral mucosa became swollen, red and ulcerated, and she could not eat. Amenorrhea had been present for four months.

She was well developed and pale, and too weak to stand. A "butterfly-shaped," erythematous, squamous lesion over the bridge of the nose and on the malar regions was sharply demarcated from the normal skin (figure 87). From 10 to 12 similar lesions, each about 2 cm. in diameter, were present on the anterior portion of the neck and in the sternal region. There were several ulcerated lesions on the roof of the mouth and on the tongue (figure 88). The ankles showed pitting edema.

The erythrocyte sedimentation rate was 51 mm. per hour. Peripheral blood values were essentially normal. Urinalysis showed: albumin 4 gm. per liter, red blood cells 3 plus, white blood cells 3 plus, hyaline casts and granules. Total serum protein was 4.1 gm. per cent, albumin 2.0 gm. per cent, and globulin 2.1 gm. per cent.

She was given 2300 clinical units of ACTH intramuscularly in divided doses in a 28 day period. After four days there was less scaling of the face and neck lesions (figure 89). Tongue soreness diminished on the eighth day and she was able to eat solid food for the first time in more than a month. The joint pains disappeared, and two days later her mouth and tongue were healed completely and she began eating tremendous amounts of food compared with her intake before treatment (figure 90).

After three weeks of ACTH therapy, only slight redness of the skin lesions remained. After three more weeks her skin appeared more normal, her sense of well-being improved remarkably and she became a happy, smiling girl. Urinary findings gradually became normal. The sedimentation rate remained essentially unchanged. Normal menstruation began two

months after therapy was discontinued.

During the first 30 days of therapy the daily urinary output varied between 500 and 1500 cc., edema of the lower extremities persisted, and her weight increased 13 pounds. On the thirty-first day the urine output increased to 2000 cc. Thereafter the edema gradually subsided and her weight returned to the initial level within the next month.

Since leaving the hospital four years ago, she has had 20 relapses. Figure 91 shows the appearance of an early lesion. Prompt and adequate therapy has prevented her relapses from being serious enough to require hospitalization. Her symptoms simulate the initial attack, however, and in many instances the lesions have appeared at the same sites. In 11 relapses she was treated with pituitary ACTH, in seven with cortisone and in two with compound F.

Interestingly, the lupus erythematosus (L.E.)

Figure 87

Figure 88

Figure 89

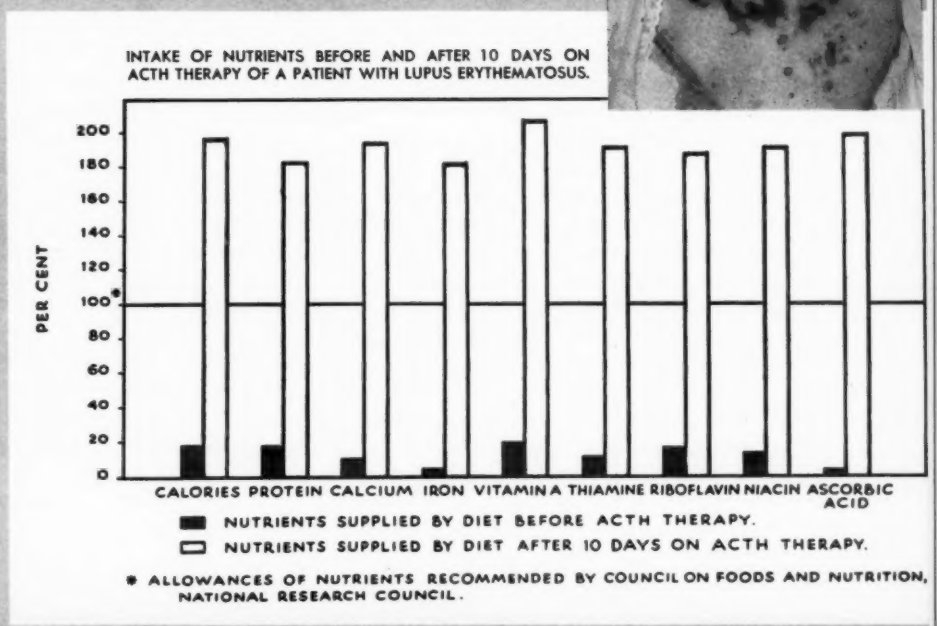

INTAKE OF NUTRIENTS BEFORE AND AFTER 10 DAYS ON ACTH THERAPY OF A PATIENT WITH LUPUS ERYTHEMATOSUS.
PER CENT
200
180
160
140
120
100*
80
60
40
20
0
CALORIES PROTEIN CALCIUM IRON VITAMIN A THIAMINE RIBOFLAVIN NIACIN ASCORBIC ACID
NUTRIENTS SUPPLIED BY DIET BEFORE ACTH THERAPY.
NUTRIENTS SUPPLIED BY DIET AFTER 10 DAYS ON ACTH THERAPY.
* ALLOWANCES OF NUTRIENTS RECOMMENDED BY COUNCIL ON FOODS AND NUTRITION, NATIONAL RESEARCH COUNCIL.

Figure 90

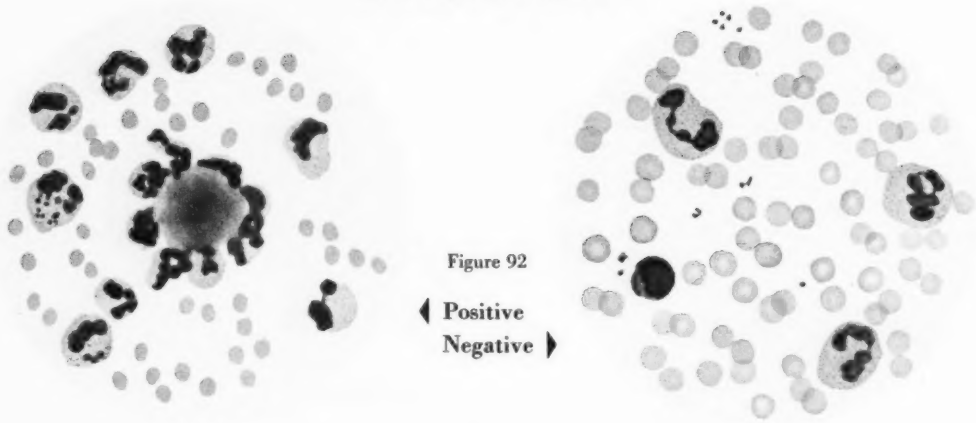



Figure 92

Contrast the difference between the positive L. E. cell phenomenon and the normal. Note the deeply stained amorphous mass surrounded by polymorphonuclear neutrophils.

Figure 91

Figure 93

cell test becomes negative following administration of ACTH, cortisone or compound F, and positive again after their discontinuance and before symptoms recur. Note the difference between the positive L.E. cell phenomenon and a negative L.E. cell test in figure 92, and the deeply stained amorphous mass surrounded by polymorphonuclear neutrophils.

The improvement in this patient can be seen in figure 93. The "moon face" is due to the heavy therapy given just before the picture was taken. Response in such cases is not uniform, and in some cases is not satisfactory, yet no other therapy available is as satisfactory.

Comment—This case and that of pemphigus which follows represent a group of carefully selected patients with whom we proceed with treatment rapidly but with caution after every effort to rule out serious contraindications and to prevent serious undesirable effects. As with all patients receiving cortisone, ACTH or compound F, frequent determinations of body weight and blood pressure, examinations of the urine, and appraisal of emotional status are made. While we do chemical analyses of the blood, urine and tissues for reasons of research, many of our patients could be treated without these analyses.

# pemphigus

## Case Thirty-One

A 29 year old man came to the clinic complaining of "blisters" of the skin which followed even slight trauma such as an insect bite. He stated that two sisters had similar "blisters" and another had asthma. His skin had not been clear since he was six years of age. The affected area became pruritic and painful for about four days, then a blister formed and the itching subsided. Occasionally a blister broke and the skin became infected. "Corns" developed on the palms, fingers and feet when he was 11 or 12 years old. Lesions were less numerous and less severe during the winter. Usually he felt tired and drowsy when the blisters were forming. The foot lesions sometimes became so severe he could not walk, and at times he was so uncomfortable that he could not work at his job as a lumber checker. Because of the itching, stinging and discomfort of the lesions, he could sleep very little. The many ointments and medicines which he tried gave him no relief.

Figure 94

He was small and underweight, and appeared depressed, apprehensive and chronically ill. Over the dorsa of both hands were several blebs varying from 1 to 6 or 8 cm. in diameter, clear to slightly pink in color, and many recent blebs which were healing (figure 94). On the left foot and ankle there were one large bleb and several other eruptions. Several blebs and a number of areas representing various stages of healing were scattered over the back and abdomen. The blebs had no surrounding area of redness and no swelling. The fingernails were thickened and ridged.

Confluent elevated areas of hyperkeratosis distributed over the course of the tendons of both palms extended out to the fingertips (figure 95). There was also some hyperkeratosis of the lateral aspects of the ankles. The skin of the legs was rough and scaling. Uniform, apparent atrophy of the muscles of the lower extremities was particularly noticeable on the right foot about the ankle. There was some tightness and induration of the skin of the legs, feet, forearms and hands, but he had full range of movement of the joints. Laboratory findings were essentially negative.

During a period of 16 days he received a total of 1,675 mg. of cortisone administered in divided doses. On the third day of therapy he felt better, and on the fourth day his skin was softer with less itching and pain, and he slept much better. The blebs oozed less and healing was apparent. The next day no new blebs appeared (figure 96) and the patient stated that he could not remember ever feeling better. Facial improvement was particularly noticeable, and he was able to shave a larger area than ever before.

Figure 95

laughingly complained that the treatment had been expensive.

This patient has had many relapses, and treatment is initiated when symptoms begin to appear. He has received ACTH and compound F, both of which produce improvement similar to that following cortisone therapy. After each course of treatment he returns to work and continues for weeks and sometimes months without further treatment.

Comment—This patient's lesions are associated with very minor traumas, and the skin seems to have a somewhat limited capacity for regeneration. We do not understand the mechanism by which these hormones suppress the blebs. Heavy treatment tends to lessen the number of lesions which follow the trauma resulting from his work.

Figure 96

During therapy and for two weeks afterward, he felt well, and only an occasional bleb appeared following a mosquito bite. Then he began to lose energy and feel drowsy. His appetite decreased, itching of the skin returned, and he was unable to sleep well. Blebs appeared more frequently, but he volunteered that he still was much better than he had been prior to therapy. His blood pressure, which was 80/50 before therapy, rose to 118/60 on the second day of therapy and ranged between this level and 120/70 throughout the course and for about three weeks thereafter, and then gradually decreased.

This patient was so underweight and emaciated when first seen that he bought his clothes in the children's department; after treatment he bought them in the men's department. He

Frequently, antihistaminics aid in the treatment of dermatoses which tend to run a self-limiting course. Contact type dermatitis may be relieved by one of the antihistaminic drugs, and we use these materials effectively in some cases. However, a short course of cortisone, ACTH or compound F is even more effective in many instances. Acute urticaria, angioneurotic edema, drug eruptions, multiform erythemas and eczema may respond well to therapy with these hormones. The following case is representative:

**Case Thirty-Two**

# allergic dermatitis

A 78 year old white woman came to us with burning, itching and swelling of the left side of her face and forehead and the left eye. Similar symptoms 17 years previously had involved the neck, shoulders and arms. Various types of therapy were tried, and it was not until her physician discovered that the lesions were aggravated when she wore a certain blue dress and advised her to stop wearing it that the lesions gradually healed. Fourteen years later arthritis of the knees and shoulders developed and was relieved by salicylates.

Shortly before we saw her, the skin of her left thumb and forefinger became red and "blistered." She thought she had burned her hand and applied several ointments which caused even greater irritation. Two days later an area of erythema and swelling appeared in the left malar region and spread rapidly to involve the left eyelid and forehead (figure 97). Calamine lotion produced greater burning and itching and increased the erythema.

Questioning disclosed that she recently had been knitting with blue wool; we advised her to discontinue using the wool. Two large doses of ACTH were given intramuscularly. Sixteen hours after the first injection the lesions seemed to be localizing, with less swelling, itching and erythema. After two days on ACTH the lesions had almost disappeared (figure 98).

Comment—Injections of ACTH relieved the allergic dermatitis promptly, with no undesirable symptoms and no relapse or recurrence following cessation of therapy. Similar cases have responded equally well to oral cortisone or compound F. Compound F is about 35 per cent more effective per unit of weight than cortisone. Therapy with any of these agents should be highly individualized.

Figure 97

Parenteral and oral compound F and cortisone are much better known than these agents in ointments. Since 1949 we have studied intensively the local application of cortisone, and more recently of compound F, in iritis, uveitis and many skin diseases in an effort to understand the pathogenesis of these diseases. From our observations and the extensive studies of Sulzberger it would appear that the current conceptions of the action of ACTH and cortisone are oversimplified and seriously restrict our day-to-day thinking.

Although cortisone used topically is effective in some cases, compound F is so much more efficacious locally that we will limit this discussion to the latter agent. Either material can be effective without any measurable or detectable systemic changes.

After many trials we learned that ointments containing more than 2.5 per cent compound F or cortisone have little or no more value than those containing 1.5 or 2 per cent. We have used successfully ointments containing 5 per cent or even more, but prefer more frequent applications of lower concentration. At a concentration of less than 1 per cent, many lesions which can be ameliorated are ameliorated slowly or not at all. Hence the most effective range is from 1 to 2.5 per cent. Some patients prefer creams and others, ointments; some dislike the oily base, and others refuse it.

Figure 98

We observed all our patients daily and found that much relief may come within 24 to 48 hours, although reduction of itching, burning and discomfort tends to be more gradual. In a few patients, lesions flared up while they were using the ointment even after a satisfactory response, but improvement was maintained with continuous use. When a lesion is acute, we recommend four applications a day, although two are often adequate. In acute, self-limiting disease we have the patient discontinue the ointment as soon as possible; in chronic conditions, we have him continue using it.

Our patients have been given various other topical medications, and without exception they agree that the hydrocortisone preparation is the most effective. Patients with atopic dermatitis, pruritus ani and pruritus vulvae obtained remarkable relief, sometimes greater with the ointment than with oral administration. The ointment is sometimes effective on one lesion and ineffective on another on the same patient. A good response is accompanied by improved general condition; the patients eat and sleep better as their lesions clear. No adverse systemic effects or chemical evidence of local adverse effects have been noted. Infants, adolescents and older persons are included in this group. The cleanliness, ease of application and relief of the burning and stinging appeal especially to children.

Persons allergic to other topical medications have not become sensitized to these preparations. One patient with chronic allergy to various substances has used 16 oz. of 1 per cent compound F ointment over a period of three months. The material has been "rubbed into the skin well" all over her body, with almost complete disappearance of her sensitization and no adverse systemic or local effects as long as she continues its use. "The trouble starts back" within a few days of stopping the treatment. Even the first patients treated with this preparation still respond to it. Compound F and cortisone ointments produce no disagreeable symptoms, do not stain body tissues or clothing, and do not have a disagreeable odor.

To summarize, an ointment of hydrocortisone, ranging from 1 per cent to 2.5 per cent, is much more effective than a similar ointment of cortisone when used topically in the treatment of selected diseases of the skin. A potent ointment will relieve the pain and disability of countless human beings ranging in age from infancy to old age, and bring new hope. Sulzberger, ourselves and other investigators have found that fluoridated compound F in ointment form is 10 times as efficacious as is compound F per se.

## Case Thirty-Three

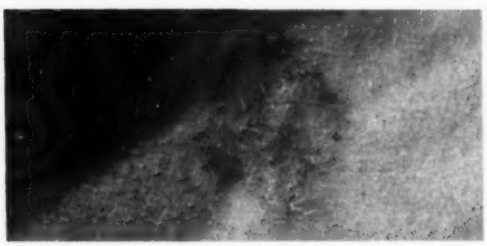
# *allergic dermatitis*

## DUE TO WRIST WATCH

This is a case in which the specific irritant was known. A 42 year old woman developed the lesion shown in figure 99 after two or three hours' contact with a wrist watch. Response was prompt following application of compound F ointment. In such cases we advise the patients to avoid as much as possible the specific irritants which cause the reaction.

Comment—Ordinarily these acute nonfatal reactions are self-limiting, but application of compound F is most effective in giving prompt relief. The variability of these conditions from patient to patient is so great that one cannot predict which patients will have such dramatic benefit. After a precise diagnosis, a short intensive period of therapy will convince even the most skeptical physician that many of his patients with similar conditions can be aided. In many instances, local application of compound F ointment seems to correct a cell deficit, but the disease itself is not eliminated. The lesions will reappear if contact is made again with the irritants. Yet these chemical agents which now have been made artificially do give the affected cells a method of responding against the causative agent.

Figure 99



The principle that the symmetry of pellagrous dermatitis depends on similar nerve and blood supplies and equal risk of the two sides of the body to the trauma of everyday living has been well established. However, we have tried to understand the mechanism which causes skin lesions to develop asymmetrically. The case which follows supports our theory that an inefficient blood supply might be a strong predisposing factor. At the site of the lesion there seems to be a discrepancy between local metabolic needs and what the blood supplies, thus interfering with body chemistry. Compound F ointment acts at a cellular level by supplying local tissue demands during cellular stress. The physician must study the patient carefully to determine if elimination of a coexisting disease will eliminate the trouble.

## Case Thirty-Four

# *dermatitis* SECONDARY TO VARICOSE VEINS

Figure 100

Figure 101

A 52 year old white woman came to us with "breaking out" on her right foot and ankle. She thought it was aggravated by water and certain soaps. Her physician told her she had eczema, and she had tried many ointments without relief. The itching and burning made it difficult for her to rest at night. The affected area measured approximately 3 by 5 inches, was slightly elevated, denuded and partially crusted (figure 100). She had mild but definite varicose veins in this leg.

She was first treated with a 2 per cent cortisone acetate ointment. Gradually the erythema and itching subsided and the lesion became slightly smaller. Six weeks after treatment was discontinued the lesion was back to its former size. She then was given 1,675 mg. of cortisone acetate intramuscularly over a period of 75 days. Again there was relief of the burning and itching and a decrease in size of the lesion, and again, six weeks later, itching and redness returned. Compound F ointment was then used, and there was much more prompt and complete relief (figure 101). As long as she used the

ointment four times a day she remained free of symptoms. Six weeks after we discontinued therapy with compound F ointment, because of a shortage of material at that time, the condition recurred. We recommended that she have her varicose veins treated, which she did. Since then the lesion has not recurred.

Comment—Permanent rehabilitation has occurred in this case. Although it is not always possible to find and eradicate the primary cause, patients can, in many instances, resume work and a normal way of life. The disease is not eliminated by hormonal therapy; the hormones muster the chemical forces of the body against the inciting factors. Compound F was somewhat more effective per unit of weight than cortisone when administered orally, and much more effective when given locally as an ointment.

Figure 102

Figure 103

# DERMATITIS, PROBABLY OF EMOTIONAL ORIGIN

A 61 year old white woman came to the clinic complaining of itching and burning of her skin. She had been in good health until her husband died, when she became nervous and emotionally unstable and had "hives" for the first time in her life. A severe rash around her left ear cleared following use of an antihistaminic ointment. After about a year, the ointment no longer was effective and the rash spread over her neck and face to the left eyelid. The intense itching, burning and pain interfered with her sleep.

Intramuscular injections of 100 mg. of cortisone each day for 11 days gave relief. Ten days after therapy was discontinued and the swelling had subsided, it began to recur. One week later it was beginning to crust up behind her ear (figure 102). Compound F ointment then was applied four times a day for two weeks, and there was remarkable improvement (figure 103). She has continued using this ointment twice a day, and symptoms have not returned for six months. She sleeps better, eats more and is able to work and take care of herself.

Comment—All our cells and tissue fluids contain sodium and potassium. Their precise role is not completely clear; however, ACTH, cortisone and compound F profoundly influence their metabolism. Among the tissue fluids which we studied in this case and others in which parenteral injections of cortisone, ACTH or compound F were given is saliva. A lowered concentration of sodium in human saliva follows repeated intramuscular injections of a sufficient amount of these hormones, although that of potassium is not materially altered. Local applications of these hormones produce no change in concentration of potassium or sodium in the salivary secretion or any other tissues or fluids.



Case Thirty-Five

## Case Thirty-Six *purpura* DUE TO DECREASE IN THE NUMBER OF BLOOD PLATELETS

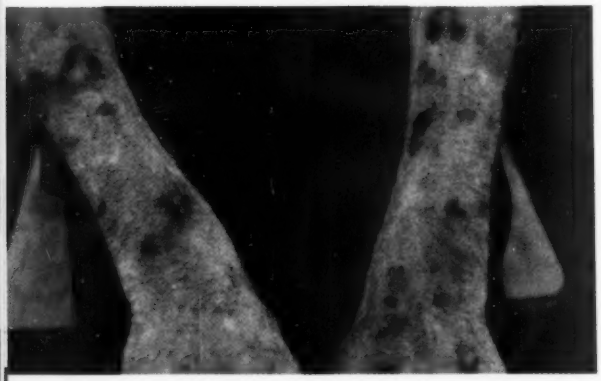


Figure 104

A 50 year old white man who bruised easily came to the clinic seeking relief. A few years previously he had noted that trauma was followed by an abnormal amount of bruising (figure 104). He had been in good health prior to this, there was no evidence of allergies or anemia, and his platelets were decreased in number. He was given 100 mg. cortisone orally each day, and the purpura disappeared within three weeks. Treatment was stopped, and about a year later the lesions recurred. He was treated with 65 mg. of compound F orally each day, with similar results.

Comment—Purpura is due to a decrease in the number of blood platelets and is caused by many different hemorrhagic disorders. The most frequent type is associated with infectious disease. The bleeding associated with jaundice is relatively common and is due to lack of vitamin K with an associated decrease of prothrombin in the circulating blood. The incidence of idiopathic thrombopenia purpura is low—some 2 or 3 per cent of all cases. In the next section we will describe cases of anemia with purpura which respond to various antianemic substances. The clinical lesions appear identical to those of this case.

## Case Thirty-Seven *loss of skin elasticity*

A 30 year old white woman was in good health until after puberty, when pellagra developed in association with chronic nutritive failure. The skin lost its elasticity due to malnutrition (figure 105). Several observers estimated this patient's age as 20 years more than her actual chronologic age. This case illustrates that the lack of chemicals resulting from a habitually poor diet affects skin elasticity.

Comment—Here is an example of the effect of poor nutrition on the skin which can be seen with the naked eye. The nutrients ebb and flow into the tissue spaces, but when the supply of nutrients is insufficient or when the body no longer uses them properly, many symptoms develop. We must learn what goes on and how to correct malfunctioning. We believe it can be corrected chemically.

In the next section we shall see how certain chemical substances affect selected cells of the bone marrow to relieve blood dyscrasias, and of the brain to relieve psychotic symptoms.

Figure 105

# NUTRIENTS IN CONVALESCENCE AND REHABILITATION

It is a fundamental biologic phenomenon that organisms, whether one cell or more, are composed of cells which arise from preexisting cells. What is this process that starts and maintains the chemical reactions that result in the formation of cells and the elaboration of new protoplasm, and why does it not always satisfy functional needs? All too commonly, disease occurs. Physicians have always sought to ease pain and disability and to discriminate between foods that are good for patients and those that are not. Progress has been made not only through careful observations but also through trial and error.

Brilliant nonmedical investigators have aided the practicing physician. Like the practicing physicians, many of these investigators have been much concerned with illness. Dr. R. R. Williams, in accepting the Willard Gibbs award, referred to his early contact with beriberi as follows: "In short, beriberi was a principal topic of conversation in scientific and medical circles in Manila during those early years of my enlistment with Vedder in the Philippines."

Those of us who are now concerned with the problems of chemical deterioration and how it can be chemically predicted and rectified are indebted to many famous clinicians who have described their findings. In the picturesque words of C. Lombroso: "If you should traverse the hills of Brianza and Canavese, you would most likely meet some pitiable wrecks of humanity, with eyes fixed and glassy, with pale and sallow faces and arms fissured and scarred as by a burn or large wound. You would see them advancing with trembling head and staggering gait like persons intoxicated or, indeed, as though impelled by an invisible force, now falling on one side, now getting up and running in a straight line like a dog after its quarry and now again falling and uttering a senseless laugh or a sob which pierces the heart—such are the pellagrins, poisoned by the toxins of spoiled Indian corn."

The effect of inadequate nutrition on the nervous system has assumed increasing importance as a result of the rapid accumulation of clinical, experimental and pathologic data. The isolation, recognition and artificial synthesis of a number of components of the vitamin B complex have made available adequate amounts of pure crystalline material for clinical research.

Lombroso's explanation of the mental symptoms of pellagra is simple, though incorrect; unfortunately, he did not know what nicotinic acid could do for the pellagrin. It is difficult to evaluate the status of a nutritional deficiency in man, even when there are no associated mental changes. Even the lay observer associates mental changes with endemic pellagra. The more serious mental involvement manifests itself as various psychoses: loss of memory, disorientation, confusion, excitement, mania, depression, delirium and paranoia.

Patients with pellagra may have delusions ranging from ants, insects and worms to hatchets and knives. Skin lesions may be associated in their minds with insects, pain or filth; crawling sensations and burning pains may be associated with spiders or nettles. These symptoms often precede mania, but are not necessarily associated with a true pellagrous dementia or dermatitis. These patients do not respond well to "psychiatric" treatment and they are made worse by administering large amounts of carbohydrates or medicines that are not antipellagric. It is significant that pellagra patients generally have poor eating habits.

## Case Thirty-Eight

# pellagrous psychosis

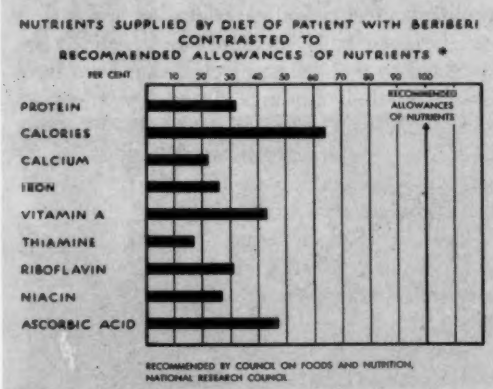
A 31 year old Negro woman complained of weakness and diarrhea of five and a half months' duration. Although the symptoms were insidious in onset, she did note gradual weakness, intermittent diarrhea, abdominal discomfort, loss of weight, and increased pigmentation, roughness and induration over the elbows; she could remember no sequence of these symptoms. Anorexia, nausea and vertigo developed.

Physical examination showed her to be well developed but poorly nourished. Pellagrous lesions were seen on the elbows (figure 106), and the legs were swollen due to fluid retention. She was disoriented as to time, reacted sluggishly, and could not recall even recent events. There were periods of visual and auditory hallucinations, insomnia and confusion. She had no appetite. Figure 107 shows her diet.

We administered glucose parenterally, and she quickly became much worse. We then gave her 50 mg. of niacin amide each hour in glucose and kept the glucose intake constant. Within 48 hours her mental symptoms and edema had disappeared; appetite, strength and general condition had improved remarkably, and she became a responsible person.

Figure 106

Figure 107



Case
Thirty-Nine

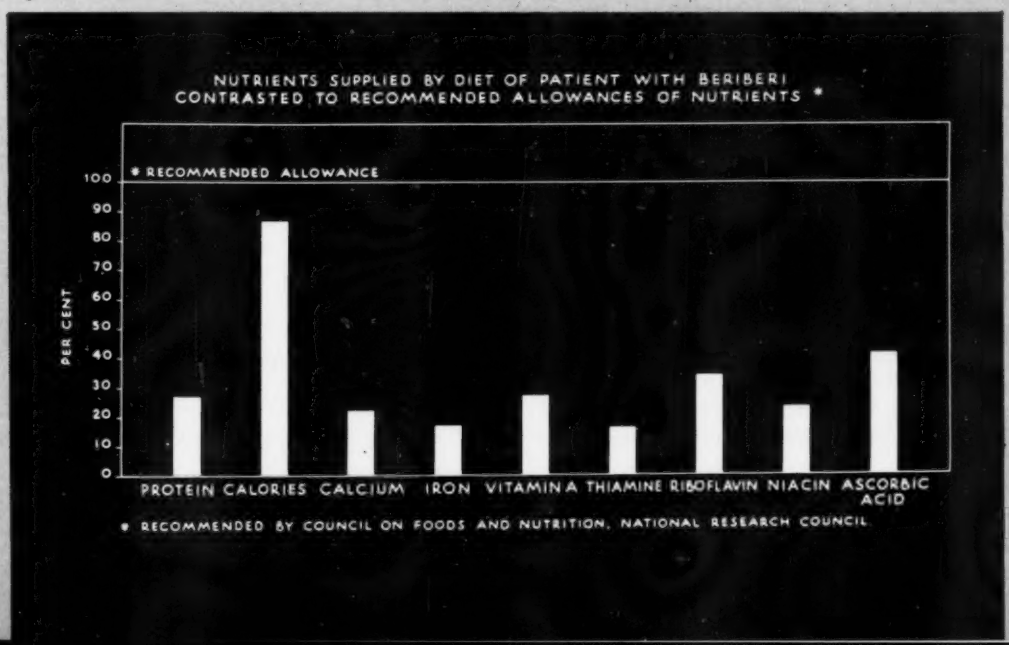
# polyneuritis

## (BERIBERI) DUE TO A DEFICIENCY OF VITAMIN $B_1$

A 40 year old white woman was relieved of pellagra after receiving 50 mg. of nicotinic acid 10 times a day. At that time there was no evidence of vitamin $B_1$ deficiency. She returned home and continued to eat her usual inadequate diet (figure 108) and to take nicotinic acid. Within six weeks mild peripheral neuritis developed; 10 weeks later it was so severe she could not sleep, and her memory became impaired. Prompt and complete relief followed the injection of 20 mg. of vitamin $B_1$ twice a day. She continued to eat her usual diet.

Comment (cases 38 and 39)—Certain patients with mental diseases or psychoses can be relieved by chemical means. Many pellagrins complain of "burning of the feet and hands" and pain and pressure over the peripheral nerves, which indicate peripheral nerve involvement. We have shown that this is a form of true beriberi. Nicotinic acid or substances which act similarly relieve the pellagra but do not affect the nerve involvement. If vitamin $B_1$ is not given and if the patient continues to eat his usual deficient diet, some impairment of memory, sharp shooting and aching pains, weight loss, general weakness, and in some instances cardiac palpitations on exertion develop. Pe-

Figure 108



ripheral nerve biopsies show that the myelin sheaths do not stain with osmic acid. At first the tendon reflexes are hyperactive, and as the disease develops they disappear. Administration of vitamin $B_1$ at this stage brings prompt improvement in sensorium, disappearance of pain, and increased appetite.

The polyneuritis of pellagra is in effect the same as beriberi, since it is relieved by large amounts of vitamin $B_1$. Beriberi and pellagra operate simultaneously in the same patient. The deficiencies of the B group of vitamins tend to be multiple; i.e., when a pure vitamin relieves certain symptoms diagnostic of the syndrome for which that vitamin is specific but does not relieve associated syndromes, and the diet remains constant, there obviously is a lack of more than one vitamin. The dietary assessment in case 39 is in keeping with this working hypothesis (figure 108).

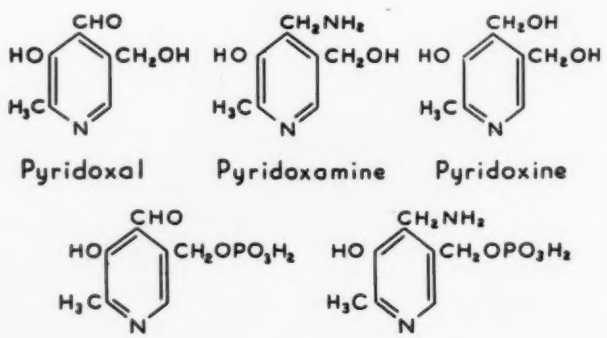
Pyridoxine has never received the consideration it deserves. It has had wide interest in animal and human nutrition since its description by György in 1934. The free and bound forms are shown in figure 109.

After we had shown that riboflavin deficiency occurred naturally in association with pellagra and beriberi, we directed our attention to vitamin $B_6$. We noted that irritability, insomnia, nervousness, vomiting, weakness, and difficulty in locomotion and coordination developed in pellagrins who received adequate nicotinic acid, vitamin $B_1$ and riboflavin but continued to eat a highly deficient diet. In 1939 we administered 50 mg. of synthetic vitamin $B_6$ parenterally to a selected group of such patients. There was prompt improvement within 24 hours, with conspicuous gain of strength and well-being and disappearance of nervous irritability and incoordination.

As early as 1940 Harriette Chick in England described convulsions in rats and pigs restricted to a diet lacking in pyridoxine. James Rinehart's work showing that monkeys on pyridoxine-deficient diets tend to develop arteriosclerosis has never received the attention it deserves. In 1950 Synderman and associates induced in a human infant convulsions thought to be due to a pyridoxine-deficient diet.

In 1951, 1952 and 1953 a mysterious and peculiar disorder of infants occurred in many parts of the United States, characterized by epileptiform convulsions unassociated with any etiologic findings. These infants had normal birth histories and grew and developed normally until four to eight or more weeks of age when sudden generalized convulsions occurred. None of them had been breast-fed (mother's milk has a high concentration of pyridoxine). They had been given a proprietary formula, consisting chiefly of defatted cow's milk, vegetable and animal fats, iron, and certain vitamins, but not containing pyridoxine at that time. When the infants were fed another milk formula or were given any supplementary food,

Figure 109




CHEMICALLY IDENTIFIED free and bound forms of Vitamin $B_6$

they became free of convulsions. In time Molony, Parmelee, Coursin and others showed that the convulsions were due to a diet deficient in pyridoxine and were relieved by substances containing this vitamin. The infants remained free from seizures as long as they obtained adequate pyridoxine.

An oral dose of 2 mg. of pyridoxine a day seems adequate to cure seizures caused by vitamin $B_6$ deficiency or to prevent seizures. Biochemically, pyridoxine deficiency can be measured by xanthurenic acid excretion following a tryptophan load.

Each person with an endemic deficiency disease has had prolonged deprivation of dietary essentials. Before the diagnostic stage is reached, much less the terminal stage, he has one or more symptoms which might be considered those of a neurosis. One must be extremely wary in evaluating in the pellagrin what might be termed "neuropsychiatric disorders." In cases of pellagra with impending relapse we have injected sterile saline without relieving the fatigue, anorexia, vertigo, palpitations, nervousness, anxiety, headaches, forgetfulness, apprehension and distractability. Yet these symptoms disappeared promptly following the addition of nicotinic acid to the injection, and all patients remained symptom-free as long as it was administered frequently. In most instances symptoms recurred if the nicotinic acid was discontinued without the patient's knowledge.

For many years psychotic changes have been associated with severe pellagra, but we have learned that subclinical and mild pellagra frequently present symptoms which are diagnosed as hysteria, neurasthenia or anxiety states. The study of thousands of cases has shown that these symptoms often have certain characteristics which are useful in an early diagnosis of deficiency disease. They disappear dramatically following specific therapy only to return eventually if the patient remains on his usual inadequate diet without a supplement.

Physicians still confuse what we call the initial nervous syndrome with symptoms of simple depression. Nearly all physicians see patients who are depressed, and their symptoms vary greatly in severity. The depressed patient with vitamin deficiency may consider suicide, and this possibility should never be ignored. Physicians who think in terms of severe depressive psychosis may not recognize early cases of deficiency disease for what they are but consider them manifestations of so-called simple depression (although we can see nothing simple about it). These patients lack almost completely the ability to hope, their fatigue is beyond comprehension, and they complain chiefly of insomnia, loss of appetite or lack of self-confidence. Often they are unable to make decisions, and on the whole they tend to hold back or minimize what distresses them. In such cases diagnosis should be precise and treatment early.

It is noteworthy that the psychoneurotic syndromes or anxiety states draw their contents from the life of the patient, i.e., from his experiences and traumas; hence the basis will vary greatly from person to person. Despite this, the mental syndromes are amazingly uniform. We have classified the common symptoms with their elementary features as follows:

1. Elementary syndrome
   a. Psychosensory disturbances
   b. Psychomotor disturbances
   c. Emotional disturbances
2. General symptoms of the central nervous system
   a. Weakness and increased fatigability
   b. Sleeplessness
   c. Headaches

The symptoms of what we term the elementary syndrome are similar to those that may be found in diseases affecting the thalamus and basal ganglia; those of the second group characteristically accompany general disturbances of the central nervous system.

The psychosensory disturbances cause these patients to dislike bright lights and bright colors. Noises annoy them to the extent that a door slamming or a child screaming produces serious emotional shock. As the disturbances become more severe, noises become unbearable, and odors so disagreeable that they produce nausea and vomiting. Odors previously unnoticed or merely unpleasant produce acute distress, and

foods once relished are disliked. Patients are "on edge" and "uneasy," and "something is bothering or hurting" them. They complain of great weakness and dizziness, and abnormal skin lesions may or may not be present.

Psychomotor disturbances likewise are pronounced, even in the early stages. Patients describe themselves as "jittery, restless on the inside and tense" or say they are "going to have a quarrel" or that "a flash of light makes me jump and twitch." Many state that they are apprehensive, and their appearance indicates an anxiety state. As a rule, the emotional reactions are increased, and they are depressed and sad. They have phobias and fears, although they make a conscious attempt to suppress them. Two-fisted men say, "I am scared to death," and yet do not understand why. They constantly expect some sort of impending disaster to occur.

The more one studies these symptoms, the more one is impressed that they are as fundamental to pellagra as are dermatitis, glossitis and dementia. Sometimes classed as physical and sometimes as mental, these emotional disturbances frequently are the only evidence of altered bodily function which is present relatively early in deficiency states. They respond to specific vitamin therapy, whereas similar symptoms occurring in persons without deficiency states do not.

Persons who express pleasant emotions do not come to us as patients; hence when we use the word "emotional" it connotes an unpleasant experience. The most frequent emotional outbursts are concerned with fear, apprehension, anger, hostility, depression, extreme sensitivity, and general emotional instability. Sometimes these persons appear to have what physicians might call "simple anxiety states," or the picture may be that of "anxiety neurosis" or "anxiety hysteria." Nearly always such persons have insight, and in discussing what we call their pseudo-hallucinations they often state, "It was just my imagination." Almost without exception, patients complain of a poor memory—a mother forgets where she left her child; a housewife cannot remember how to prepare a dish she has made many times. Saline injections produce no benefit, but administration of thiamine and nicotinic acid results in truly amazing personality changes. Within 30 minutes to 20 hours a timid, apprehensive, shrinking person becomes a smiling and cooperative individual.

We demonstrated that in neuropathy of vitamin $B_1$ deficiency associated with endemic pellagra, cerebral uptake of oxygen is less than normal and glucose utilization is greatly decreased. These persons also have structural changes in the peripheral nerves. These studies were the first to show that the cerebral cortex does not function normally on a chemical basis in human beings with vitamin $B_1$ deficiency. From the prompt responses one must consider that there are minimal structural changes; we call them "biochemical lesions." They are not structural to gross examination and are reversible with prompt and adequate therapy.

We have also studied patients with psychoses unassociated with clinical evidence of deficiency disease. Their response to treatment is unpredictable, irregular and not too satisfactory. Striking improvement in some cases makes us wonder if there is coexistence of a mild deficiency state and an organic psychosis. We know that cerebral arteriosclerosis eventually results in decrease in the size of the brain, narrowing of the convolutions, loss of ganglion cells, atrophy of the glia and, of course, prominence of sclerotic vessels. The patient may be irritable, obstinate, penurious and morally lax, and it is well known that he tends to have failure of recent memory. This may advance to the point of his becoming confused, agitated, paranoid or delirious.

The rising tide of longevity among our population with its accompanying tragedies increases our medical responsibility in relation to senile psychoses. We must understand what goes on and how to correct it. Many of these troubled, tired, devitalized and mentally confused older people can be aided by someone's making certain they have an adequate diet rich in vitamins and minerals in a suitable, edible form. They should have vitamins and additional medication for coexisting diseases. It must be kept in mind that they cannot be depended on to eat properly

or take medicine regularly. Detailed application means a hopeful outlook for many of them, and also that many will not have to go to homes for incurables or institutions for the legally insane.

We will comment briefly on cholesterol and its association with disease due to faulty internal glandular function. Cholesterol is extensively distributed throughout all tissues and is thought to be an essential component of all cells, although its precise function is not known. It occurs in a free form and as esters with fatty acids. Cholesterol as seen in figure 110 is an alcohol. The total quantity in man is about 0.3 per cent of the wet weight of the body, the largest amount being in the skin and the next largest in the nervous tissue. The adrenal gland has a high concentration of cholesterol (4.5 per cent), the muscle, a low concentration (0.14 per cent). In the human body cholesterol comes from biosynthesis and diet.

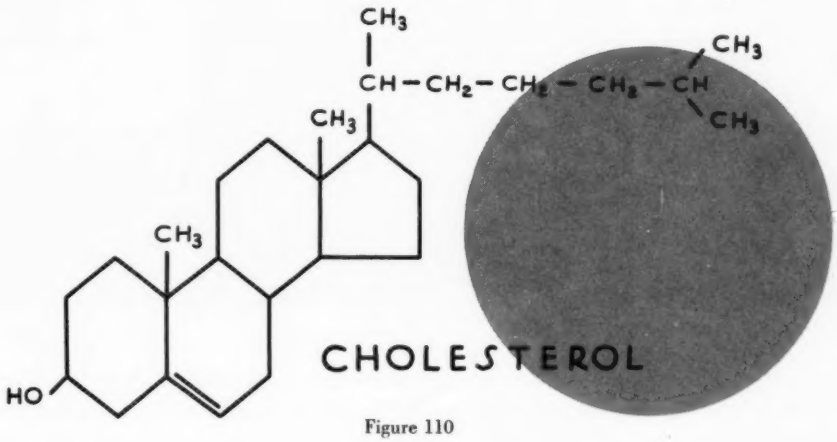



Figure 110

Does cholesterol play a key role in the transport of fat or in the functions of the adrenal gland, the nervous tissue, or the skin? What is its relation to the steroid sex hormones and the cortical hormones? Is it possible that it serves as a precursor of these hormones and of vitamin $D_3$?

A number of pathologic conditions are indicated by the concentration of cholesterol in the blood, which normally may vary from 100 to 200 mg. per 100 cc. Cholesterol is involved in the formation of gallstones and in arteriosclerosis. The sterol content of an arteriosclerotic aorta may be 50 times that of a normal aorta. There is an inverse relationship between the total blood cholesterol concentration and the degree of thyroid activity. Myxedema, which produces strange and bizarre mental disturbances, is due to hypofunction of the thyroid gland and is characterized by a lowered basal metabolism and an increased blood cholesterol. Likewise diabetics have a predisposition to arteriosclerotic changes and symptoms. In uncontrolled diabetes the cholesterol concentration is increased. During pregnancy the cholesterol content of the blood tends to increase. Pernicious and other anemias often are associated with low cholesterol values.

Normally the cholesterol content in the human body is fairly constant. Because cholesterol can be made from acetates, the dietary restrictions prescribed by many physicians are not justified, in our opinion. Some families have a hereditary tendency to maintain a high concentration of cholesterol in the blood and tissues, as shown in the following case:

# essential xanthomatosis

Figure 111

A 24 year old white man was sent to us by Dr. Louis Friedman who had found that this patient and all members of his family had a hereditary fault in cholesterol metabolism. For a number of generations, no member of his family had lived beyond 40 years, and all had died of heart disease. For four years he had noticed chest pain on exertion and that his heart "beat too fast." "Bumps" on his elbows had been present for 10 years (figure 111), and the patient said his sister also had "bumps" over her elbows and collarbone at the age of 14 years; these caused no pain. We examined the lesions of this patient and of his sister and found cholesterol crystals in them.

Various treatments brought no relief. His blood cholesterol concentration never was less than 580 mg. per cent or more than 800 mg. per cent. Choline, pyridoxine or nicotinic acid had no effect on his condition. When he was given 4,425 mg. of cortisone acetate in divided doses orally over a period of 62 days, his cholesterol dropped from 580 mg. per cent (esters 218, free 362) to 218 mg. per cent (esters 110, free 108). We did not see him again until a year later, when his cholesterol was 490 mg. per cent (esters 307, free 183). We gave him 1,525 mg. of cortisone acetate orally in divided doses over a period of 30 days. The cholesterol dropped to 220 mg. per cent (esters 150, free 70). Two weeks later it had increased to 400 mg. per cent. The cortisone had no appreciable effect on his chest pains. He decided to discontinue treatment, and eight months later he died from a sudden, acute heart attack.

Comment—The controversy regarding the role of cholesterol in the etiology and pathogenesis of disease concerns primarily the interpretation of findings in various animal experiments and an attempt to explain the discrepancy between such findings and those in human disease. In this case the dynamics of the cholesterol metabolism unquestionably were affected by cortisone. The amount of cholesterol in the tissues escapes the large safety factors and produces extensive deposits in the tissues.

Let us turn to hypertensive cardiovascular disease. Recent experience suggests that what is called hypertension is a group of diseases, running different courses. An important recent achievement is the beginning of means for differential diagnosis among hypertensive diseases. Physicians are aware that a group of substances known as adrenergic blocking agents helps rule out a pheochromocytoma, a rather rare condition. Hypertension can be relieved in many instances by surgical removal of the tumor. Many patients with hypertensive cardiovascular disease are treated with vitamins and minerals, whereas they should have digitalis, diuretics, weight-reducing diets, or some more indicated therapeutic agent.

# obesity and hypertension

## Case Forty-One

A 58 year old Negro woman who weighed 215 pounds had had shortness of breath and pain in the back of her head for a long time. Her blood pressure was 178/110 (figure 112). On a reduction diet she lost 21 pounds in five months, and her blood pressure dropped to 146/86. She has continued to lose weight, and at present, three months later, has lost another 15 pounds. Her blood pressure is 108/72.

Comment—High blood pressure is not a specific symptom or ailment; it is a sign. Many patients think their physicians should have a simple method of regulating it, of raising or lowering it at will. This woman was fortunate in that her blood pressure decreased when she lost weight, and she did not know she had had high blood pressure.

Many physicians do not distinguish between overweight, which cannot be treated by dietary measures, and obesity, which can and should be treated by dietary means. College football players, for instance, certainly would be considered overweight by standard weight tables, but none would be carrying 40 to 60 pounds of excess fat. It is said that 20 per cent of the American people are obese. We do not know what triggers the mechanism which results in overeating.

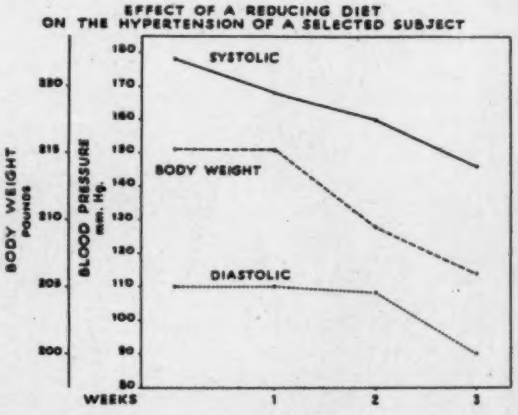



Figure 112

In studying fluid electrolyte balance we tend to pick normal healthy young males, thus avoiding the cyclic changes in women during premenstrual periods and normal pregnancy. Judicious use of modern antidiuretics is well understood. The following selected patient's recovery from heart failure is marked by diuresis and the ability to breathe more normally.

## Case Forty-Two

# cardiovascular disease and edema

A 48 year old Negro man came to the clinic complaining of orthopnea and dyspnea. When able to sleep at all, he sat up and used several pillows. Many blood pressure determinations showed an average systolic pressure of 164 and a diastolic pressure of 130. He had marked pitting edema of the lower extremities (figure 113). We asked Dr. J. M. Ruegsegger of Lederle Laboratories for 2-acetylamino-1-3-4-thiadiazole-5-sulfonamide*, a potent carbonic anhydrase inhibitor which does not have the toxicity associated with sulfanilamide administration. We gave this patient 250 mg. of this material every six hours. After 12 hours his urinary output increased and he had a complete night's sleep, the first in many months. On the third day, urinary output was 2000 cc. and he slept all night. Urinary output varied from day to day, and the edema continued to decrease (see figure 114 showing the loss of edema and the urinary output on the fifth day). Figure 115 is taken from the data of Dr. William Niedermeier of our group who made determinations on this patient. These data are similar to those of other investigations. After 10 days the dose was decreased to 250 mg. three times a day. The patient was no longer apathetic; he smiled, was jovial, and spoke about his troubles and how apprehensive he had been that he would not get well or work again. The edema continued to subside, and the blood pressure was 150/110. The future course is unpredictable.

Comment—Metabolic products contain many acid and alkaline substances which tend to change the pH range of normal body fluids. They must be buffered in the blood during their transport to the excretory organs. One of the very efficient buffer systems in the blood is the bicarbonate system. This reaction can be accelerated by a zinc-containing enzyme, carbonic anhydrase. One year later the patient still responds to Diamox by excreting sodium and water and is edema-free.

### HEMATOLOGIC FACTORS

We have mentioned that the blood carries products to be excreted; space does not permit our pointing out the glaring defects in our knowledge. We wish to emphasize, however, that study of the blood itself may reveal a true anemia, i.e., an actual decrease in the total amount of hemoglobin or the number of red blood cells in the entire body which involves a consideration of the blood volume. Excellent books on this subject by Fowler, Murphy, Sturgis and Wintrobe are available and should be consulted for classification and morphologic details. The two major pigments of protoplasm are the red "heme" and the green "chlorophyll." Both are intimately connected with the chemistry of water. No one understands why these red and green pigments are structurally similar yet different. Are they put together by the same kind of enzymes or by an entirely different system of enzymes? Hemoglobin is of the greatest importance to our lives. This large molecular protein constantly must carry oxygen to our tissues. As long as we breathe and our blood circulates, hemoglobin is necessary.

Throughout history iron has symbolized strength. In the nutritive sense, also, iron is

*Now marketed under the name of "Diamox."

important. Hypochromic microcytic anemia results from an inadequate supply of iron in the body, and therefore the amount of hemoglobin formed is below normal. This type of deficiency is usually secondary to gastrointestinal hemorrhages in the male and uterine bleeding in the female, but can occur in either sex from hemorrhages from any source. We have not seen it in the adult male as the result of a dietary deficiency, but have seen it in women who menstruate and in infants. During pregnancy the mother must supply iron to the fetus either from her diet or from her reserves. An iron deficiency is common during and following pregnancy. If the supply is inadequate for the fetus, the infant will have an iron deficiency which can be corrected only by supplementing milk feedings with iron.

Older methods of hemoglobin determination are based on visual matching and are inaccurate, since colors fade rapidly. The physician should check the smears personally so as to appraise and integrate laboratory determinations with a thorough history and physical examination. We check smears against laboratory determinations, though we use a photoelectric colorimeter, and standardize our methods against oxygen capacity of the blood.

It is estimated that the total weight of the bone marrow of an adult man is 3000 gm. It is the bone marrow that produces the blood. Since the average life span of red blood cells is about 120 days, they must be replaced constantly. Good health requires a proper balance between their production and destruction. If there is increased destruction, the body accelerates production by changing the yellow portions of the bone marrow to red portions. Blood regeneration in many persons can increase some 800 per cent. When destruction exceeds production, hemolytic anemia may develop.

From a study of the blood smear, the physician learns if the *pattern of the blood is normal or abnormal.* If abnormal, careful study and interpretation often aid in precise diagnosis and proper therapy. For physicians who rarely view blood smears we recommend a study of figures 116 through 120, drawn by Edith Neff. All the smears are from the peripheral blood and the magnification is approximately x1212.

Figure 113

Figure 114

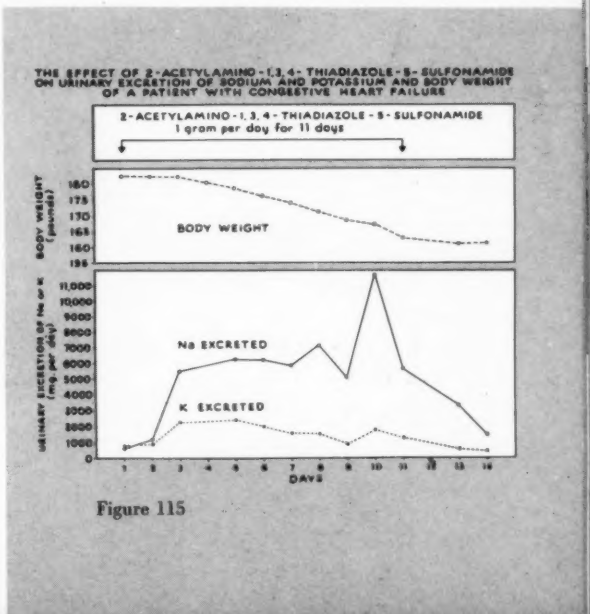

THE EFFECT OF 2-ACETYLAMINO-1,3,4-THIADIAZOLE-5-SULFONAMIDE ON URINARY EXCRETION OF SODIUM AND POTASSIUM AND BODY WEIGHT OF A PATIENT WITH CONGESTIVE HEART FAILURE
2-ACETYLAMINO-1,3,4-THIADIAZOLE-5-SULFONAMIDE
1 gram per day for 11 days
BODY WEIGHT (pounds)
BODY WEIGHT
URINARY EXCRETION OF Na or K (mg per day)
Na EXCRETED
K EXCRETED
DAYS

Figure 115

Figure 116

Iron deficiency anemia. Note the pallor in the central portions of the red blood cells and the variation in their sizes.

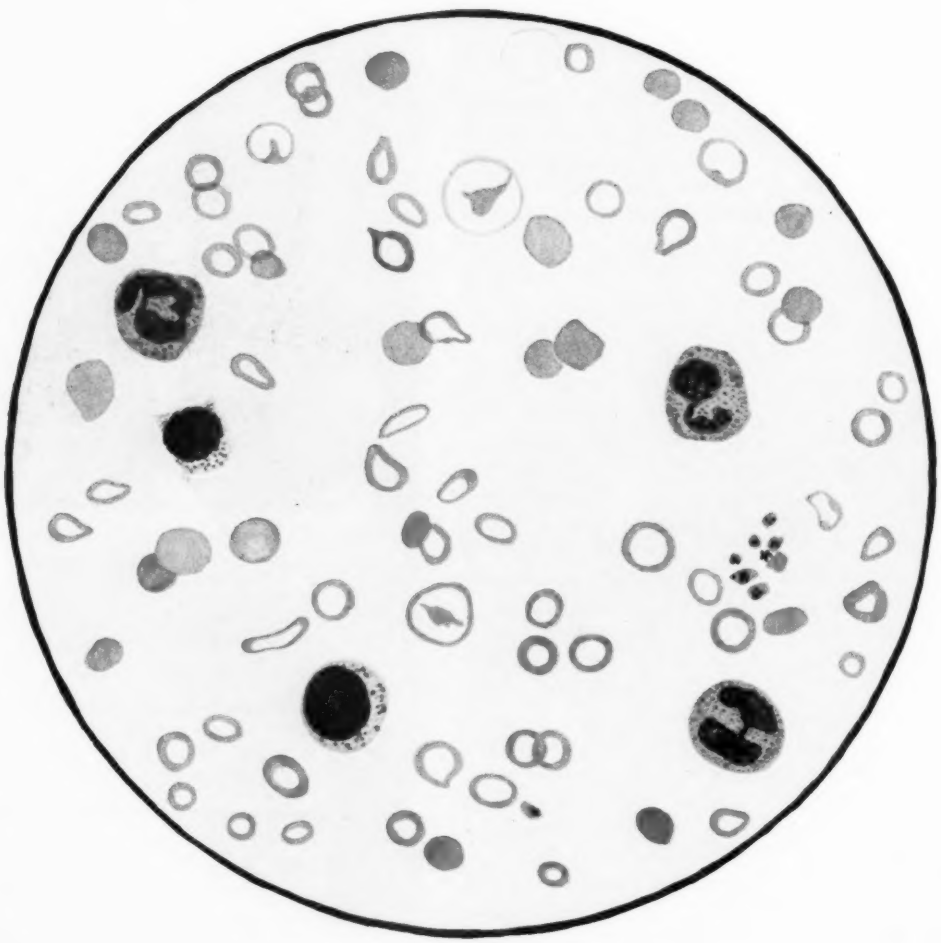


Figure 117

Sickle cell anemia (stained with cresyl blue and Wright's stain). Several reticulocytes, a number of typical sickle cells, and target cells are present.

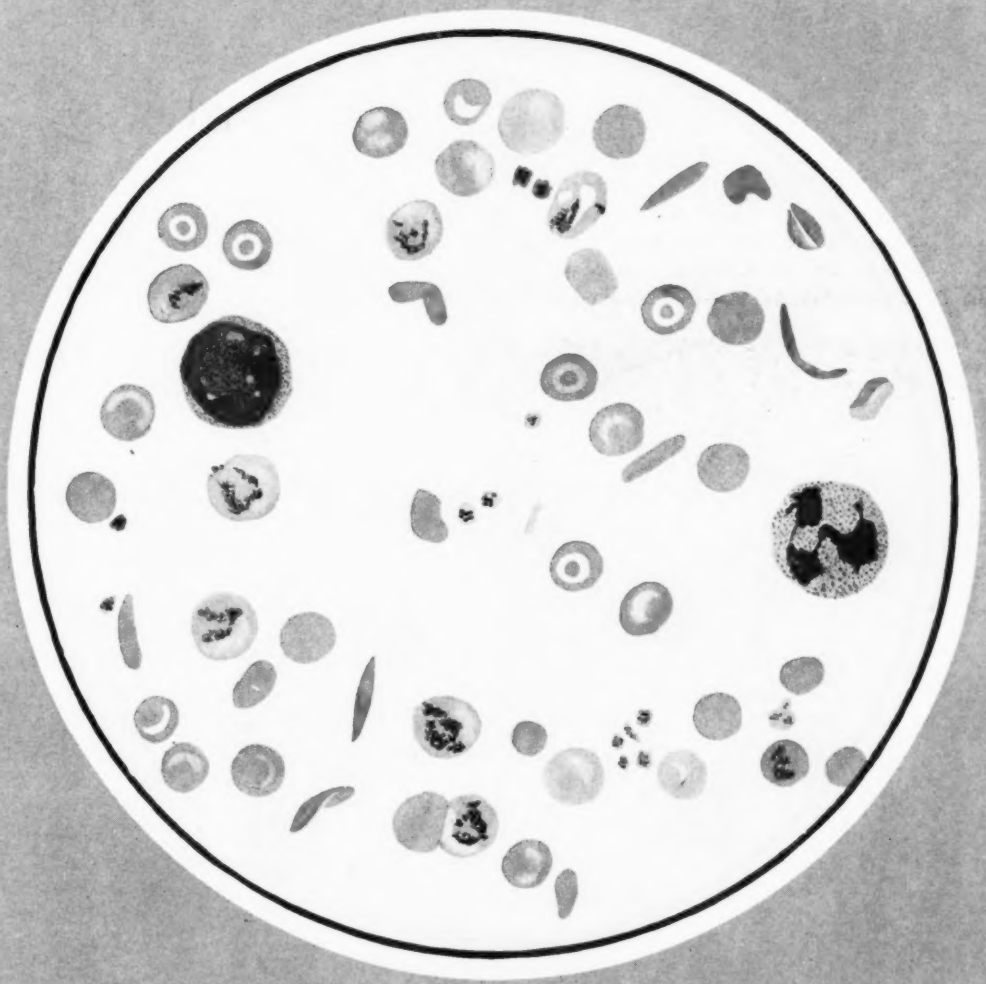


Figure 118

Nutritional macrocytic anemia. Shapes and sizes of the red blood cells vary markedly, and macrocytes are conspicuous. The same type of picture occurs in pernicious anemia and in tropical or non-tropical sprue in relapse.

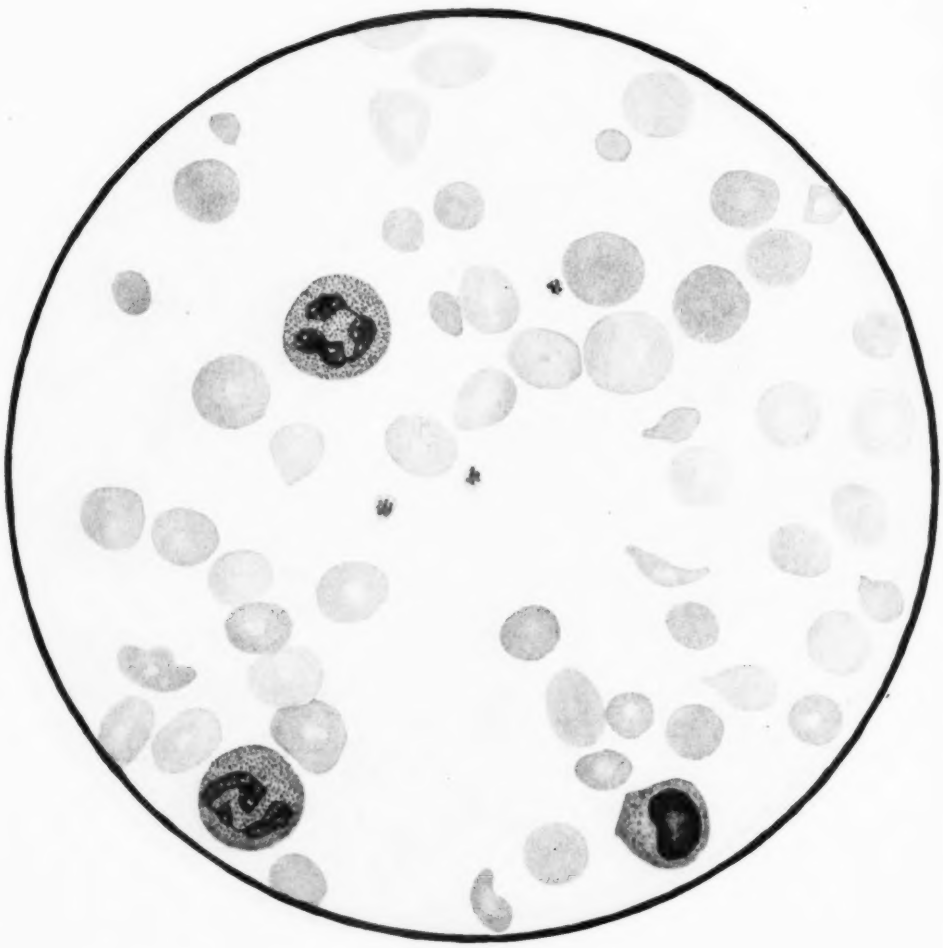


**Figure 119**

A nucleated red cell and what appears to be a rather large polymorphonuclear leukocyte. Nucleated red blood cells normally are found in the peripheral blood only in the fetus and the newborn infant; beyond that period they indicate a disorder affecting the bone marrow. An abnormal demand for red blood cells may produce an outpouring of nucleated cells into the peripheral blood. The presence of nucleated cells in association with cardiac conditions or infectious disease is much more serious than their presence in association with blood dyscrasias.

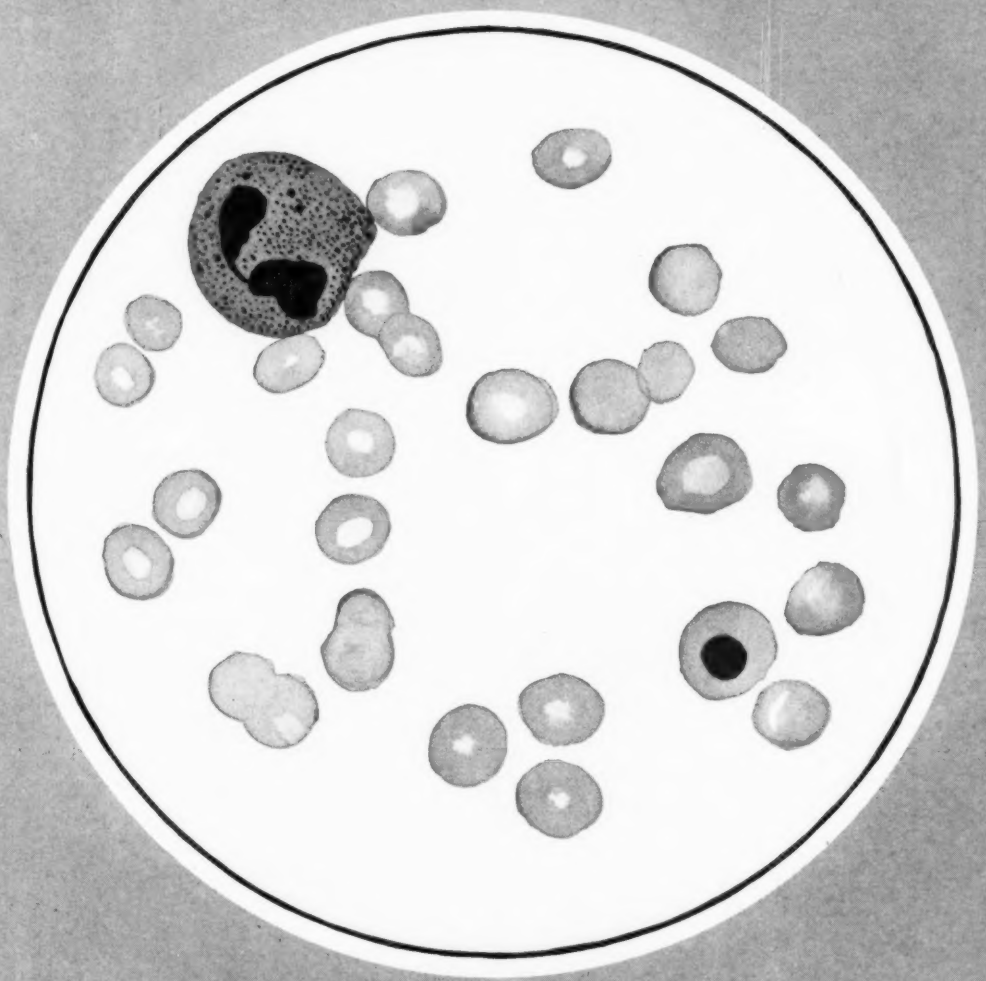
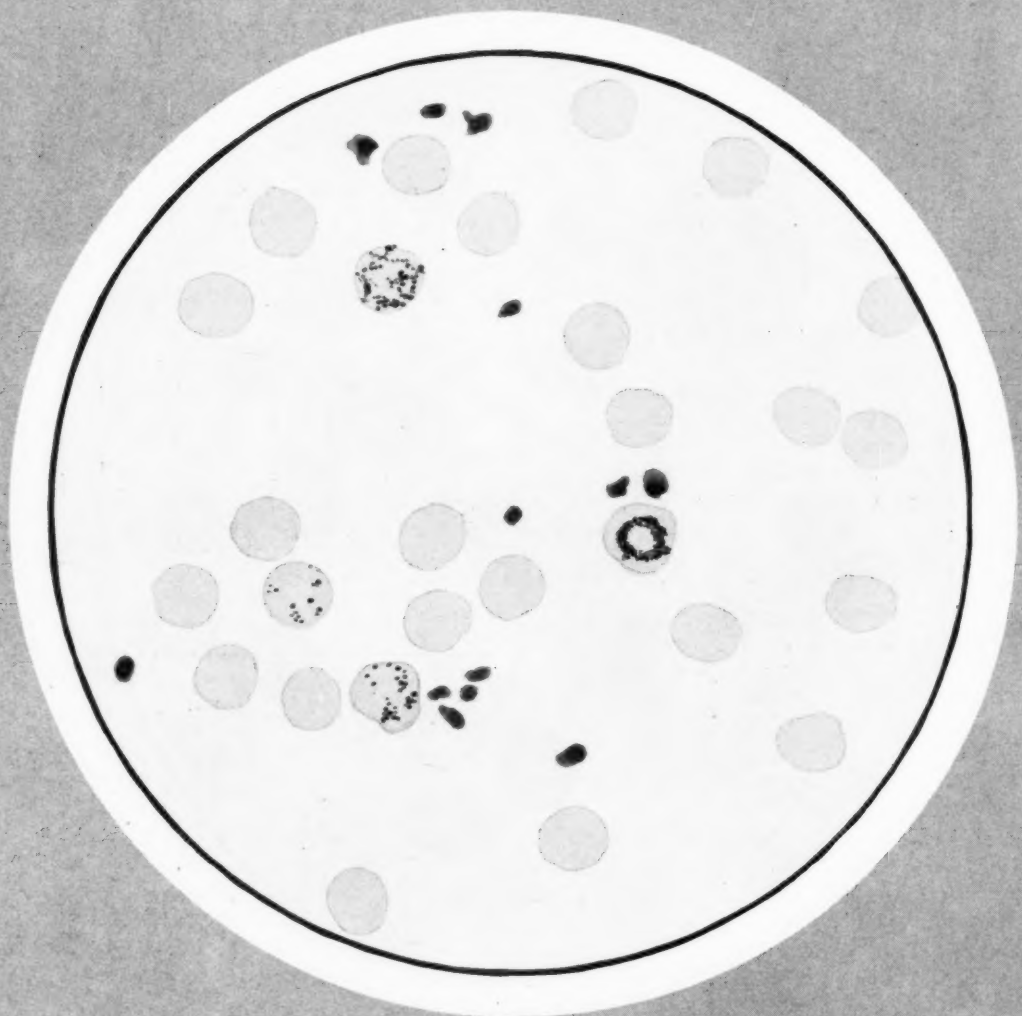


Figure 120

Pernicious anemia responding to antianemic therapy, showing reticulocytes and platelets as they appear in a moist preparation stained with cresyl blue.



The hemopoietic response to various chemical substances in a case of tropical sprue in relapse is shown in figure 121. The patient notices increased strength and well-being and develops a voracious appetite. The nutrients supplied by diet before and after vitamin $B_{12}$ therapy in a case of pernicious anemia in relapse are shown in figure 122; those in a case of tropical sprue in relapse are seen in figure 123. The nutrients supplied before and after folic acid therapy in a case of tropical sprue are shown in figure 124.

An increase in reticulocytes can be demonstrated in the bone marrow, followed soon by a great increase in the peripheral blood. The number of reticulocytes increases until they peak, and there is a striking increase in red blood cells, white blood cells, hemoglobin and platelets. An identical response is seen in nutritional macrocytic anemia and pernicious anemia in relapse.

In figure 125 can be seen some of the chemical substances found to be effective in promoting blood regeneration in pernicious anemia, nutritional macrocytic anemia, and tropical or nontropical sprue. Note the differences in the molecules. While we do not know the precise structural formula of vitamin $B_{12}$, we can make the following statements which often are helpful to the inquiring physician:

1. Vitamin $B_{12a}$, vitamin $B_{12b}$ and vitamin $B_{12d}$ are identical.
2. Vitamin $B_{12}$ contains a cyano group not present in vitamin $B_{12a}$.
3. Vitamin $B_{12c}$ has a nitrite grouping instead of the cyano group.
4. Cobalamin designates all the vitamin $B_{12}$ molecule except the cyano group. Vitamin $B_{12}$ can then be termed cyano-cobalamin and vitamin $B_{12a}$ termed hydroxo-cobalamin.
5. There are some six pseudo-vitamin $B_{12}$'s, which produce cobalt-con-

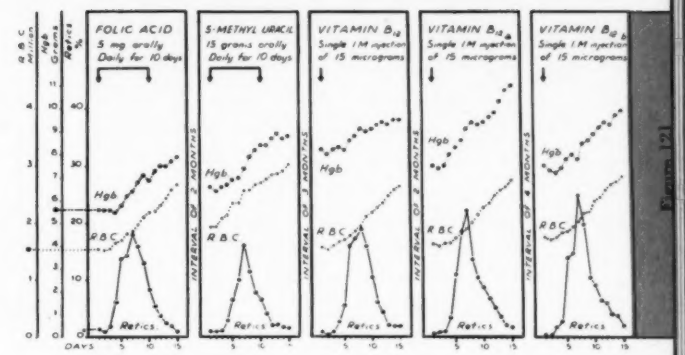
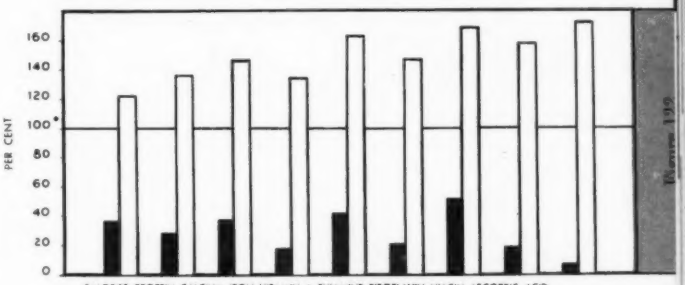
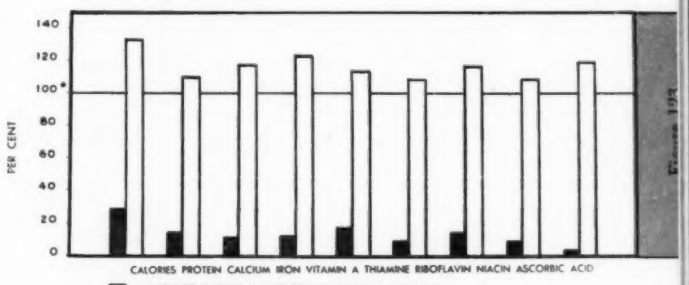
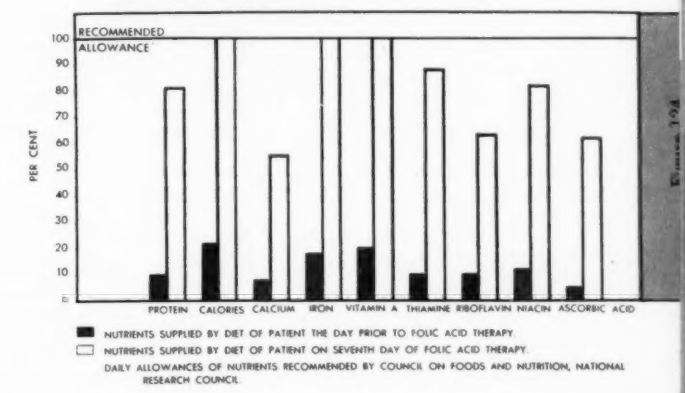


Figure 121


PER CENT
CALORIES PROTEIN CALCIUM IRON VITAMIN A THIAMINE RIBOFLAVIN NIACIN ASCORBIC ACID
NUTRIENTS SUPPLIED BY DIET BEFORE VITAMIN B12 THERAPY.
NUTRIENTS SUPPLIED BY DIET AFTER VITAMIN B12 THERAPY.
* ALLOWANCES OF NUTRIENTS RECOMMENDED BY COUNCIL ON FOODS AND NUTRITION, NATIONAL RESEARCH COUNCIL
Figure 122


PER CENT
CALORIES PROTEIN CALCIUM IRON VITAMIN A THIAMINE RIBOFLAVIN NIACIN ASCORBIC ACID
NUTRIENTS SUPPLIED BY DIET BEFORE VITAMIN B12 THERAPY.
NUTRIENTS SUPPLIED BY DIET AFTER VITAMIN B12 THERAPY.
* ALLOWANCES OF NUTRIENTS RECOMMENDED BY COUNCIL ON FOODS AND NUTRITION, NATIONAL RESEARCH COUNCIL.
Figure 123


RECOMMENDED ALLOWANCE*
PER CENT
PROTEIN CALORIES CALCIUM IRON VITAMIN A THIAMINE RIBOFLAVIN NIACIN ASCORBIC ACID
NUTRIENTS SUPPLIED BY DIET OF PATIENT THE DAY PRIOR TO FOLIC ACID THERAPY.
NUTRIENTS SUPPLIED BY DIET OF PATIENT ON SEVENTH DAY OF FOLIC ACID THERAPY.
DAILY ALLOWANCES OF NUTRIENTS RECOMMENDED BY COUNCIL ON FOODS AND NUTRITION, NATIONAL RESEARCH COUNCIL.
Figure 124

taining pigments of the vitamin $B_{12}$ group, but they contain adenine instead of 5,6-dimethyl benzimidazole in the nucleotide portion of the molecule. (The cyano group has the same relationship to pseudo-vitamin $B_{12}$ as it does to vitamin $B_{12}$ per se.)

Figure 125

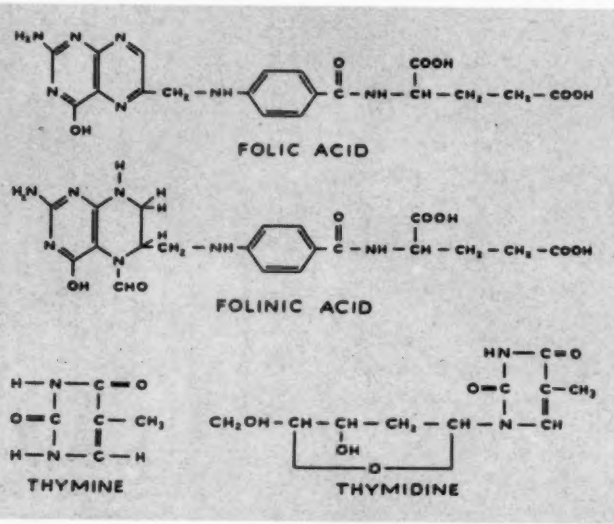


Figure 126

6. Vitamin $B_{12}$, vitamin $B_{12a}$ and vitamin $B_{12c}$ are active in producing clinical and hemopoietic improvement when injected into persons with pernicious anemia, nutritional macrocytic anemia and tropical sprue. Vitamin $B_{12}$-factor III is thought to be a metabolic product of vitamin $B_{12}$, and is active in these conditions. The pseudo-vitamin $B_{12}$ of Pfiffner and associates is inactive under the same conditions.

Figure 126 shows a Cuban patient with severe anemia characterized by a high color index and megaloblastic arrest of the bone marrow. His diet had consisted chiefly of rice, viandas (root vegetables), bread, sugar and coffee—all foods

particularly low in folic acid content. He was hospitalized and kept on a similar diet and was not allowed meat, meat products or eggs. He could not build blood on this diet until it was supplemented with 5 mg. of folic acid orally daily. The photograph on the left was made when he had a low blood count and was unable to work, that on the right after folic acid therapy when he had returned to work as a sugar cane cutter.

In figure 127 can be seen a patient with sprue, and a gallon jar containing a stool from a single bowel movement. The patient with tropical or nontropical uncomplicated sprue has severe acid steatorrhea. The typical stool is liquid and free of normal pigments, which makes it yellow to white in color. The effect of folic acid is apparent; the first part of the stool passed has no pigment, whereas in the later portion of the same bowel movement the pigments are normal and the stool is better formed in response to folic acid therapy.

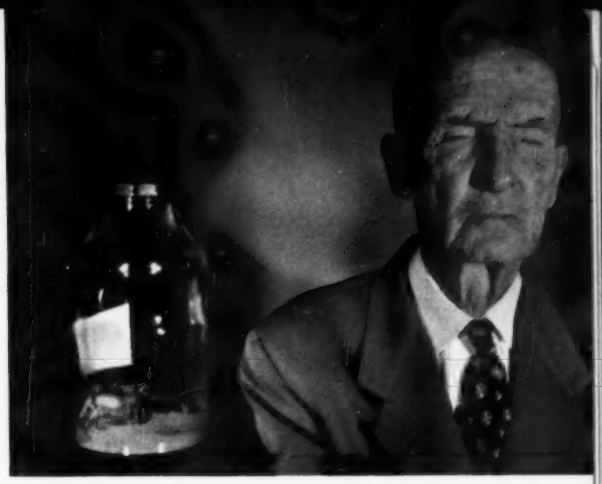


Figure 127

Figure 129

In connection with diarrheas associated with deficiency states, it is well to point out that we have tested all the antibiotics in common usage and found that they do not interfere with the effectiveness of any of the antianemic substances. For example, when a patient with tropical sprue has typhoid fever, we treat him with folic acid and chloramphenicol by mouth or with vitamin $B_{12}$ intramuscularly and chloramphenicol by mouth.

From data accumulated by us and by others on the iron salts and on folic acid and substances that act similarly, we have gained a better understanding of the interrelationships between maternal and infant blood formation. The life and health of the fetus is determined by its ability to obtain the required nutrients in the correct

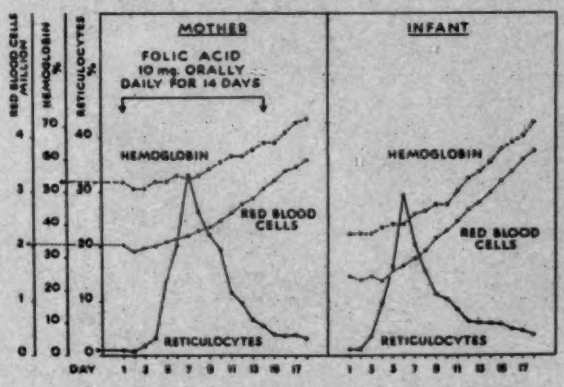



Figure 128

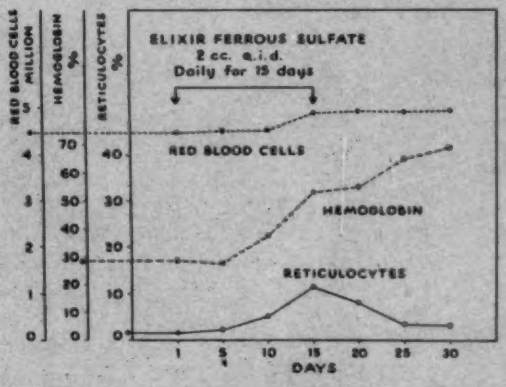



Figure 130

proportion. The health of the mother during pregnancy and in later life may be determined by her ability to provide satisfactorily for her own metabolic needs and those of the fetus. For its nutrition and excretion the fetus is dependent on the placenta.

The hemopoietic response of a mother with macrocytic anemia and that of her five month old nursing infant with megaloblastic anemia of infancy following administration of folic acid to the mother are shown in figure 128. It is clear that folic acid administered to the mother relieved not only her anemia but also the anemia of her nursing infant, thus demonstrating that this type of deficiency is a true deficiency and that an interrelationship exists between the lack of folic acid for the bone marrow of the mother and that of the infant.

Figure 129 shows a child with megaloblastic anemia of infancy who was treated with folic acid. The mother was given folic acid during three subsequent pregnancies, and macrocytic anemia of pregnancy did not develop.

The hemopoietic response of a one year old infant with iron deficiency anemia to ferrous sulfate is shown in figure 130. The mother also had an iron deficiency anemia. Note that the increase in reticulocytes is associated with an increase in hemoglobin and red blood cells. This infant was very ill, but within a few weeks after treatment was initiated, he appeared normal.

A 15 year old boy with iron deficiency anemia caused by hookworm infestation had an excellent hemopoietic response to ferrous sulfate (figure 131). This occurred without any treatment against the hookworm. Several months later, when he appeared to be in good health, he was given specific treatment for the hookworm infestation. This case demonstrates that ferrous sulfate is effective even without anti-hookworm therapy, but in general we recommend that treatment be directed against the hookworm as well as to correction of the iron deficiency.

In the past 25 years of using liver, liver extract and desiccated stomach preparations, we have observed that patients with pernicious anemia in relapse vary greatly in their responses.

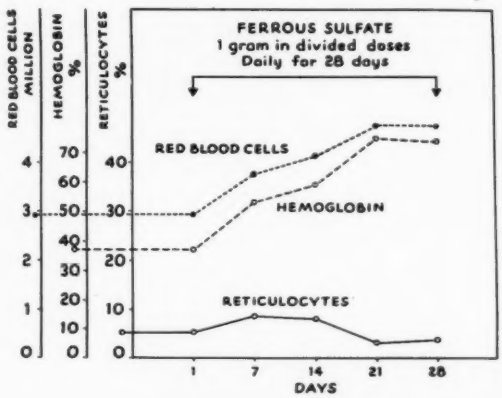



Figure 131

A parenteral dose of 1 or 2 μg. of vitamin $B_{12}$, the most potent nutrient known, will maintain a patient with pernicious anemia. Vitamin $B_{12}$ orally is relatively ineffective in tropical and nontropical sprue and ineffective in the average case of megaloblastic anemia of infancy and the pernicious anemia of pregnancy, while folic acid administered orally is effective.

A number of American pharmaceutical laboratories have made highly potent concentrates of intrinsic factor. We have tested those from Abbott Laboratories, Armour Laboratories,

Figure 132

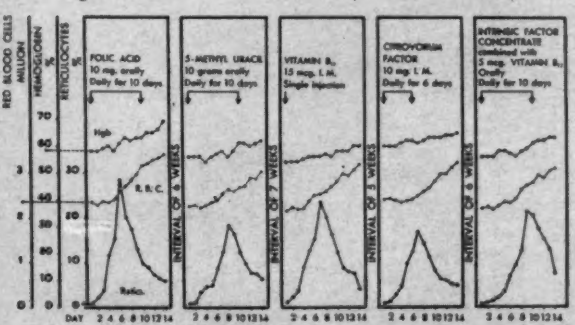
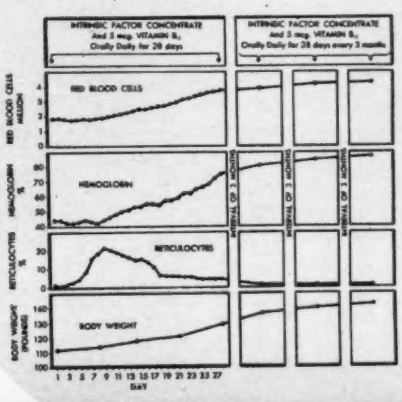



Figure 133



Lederle Laboratories, Merck & Co., Inc., Organon, Inc., Parke, Davis & Company, Chas. Pfizer & Co., Inc., J. B. Roerig and Company, E. R. Squibb and Sons, The Upjohn Company, and The Wilson Laboratories.

Anemia is only one of the important features of vitamin $B_{12}$ deficiency, and the megaloblastic arrest is only part of the bone marrow picture. The hemopoietic response in pernicious anemia to oral vitamin $B_{12}$ and a suitable intrinsic factor concentrate is similar to that which follows the administration of other antianemic substances (figure 132). The patient with pernicious anemia who responds to intrinsic factor concentrate and vitamin $B_{12}$ also can be maintained as shown in figure 133, which shows the hemopoietic response and weight gain over a period of one year. Response to the same intrinsic factor concentrate and vitamin $B_{12}$ is not as good in tropical sprue or nutritional macrocytic anemia in relapse (figure 134).

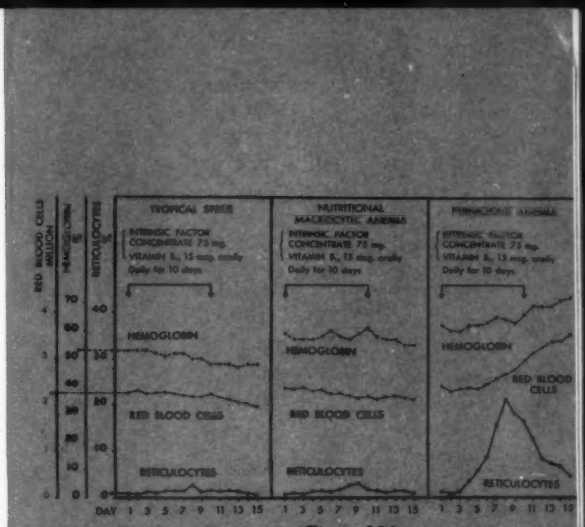



Figure 134

We shall leave the discussion of pernicious anemia with the remark that the disease is no longer pernicious.

## SKELETAL AND SOMATIC GROWTH

Mean weight curves of young white rats restricted to a representative diet eaten by Cubans with tropical sprue; effect of replacement by stock diet.

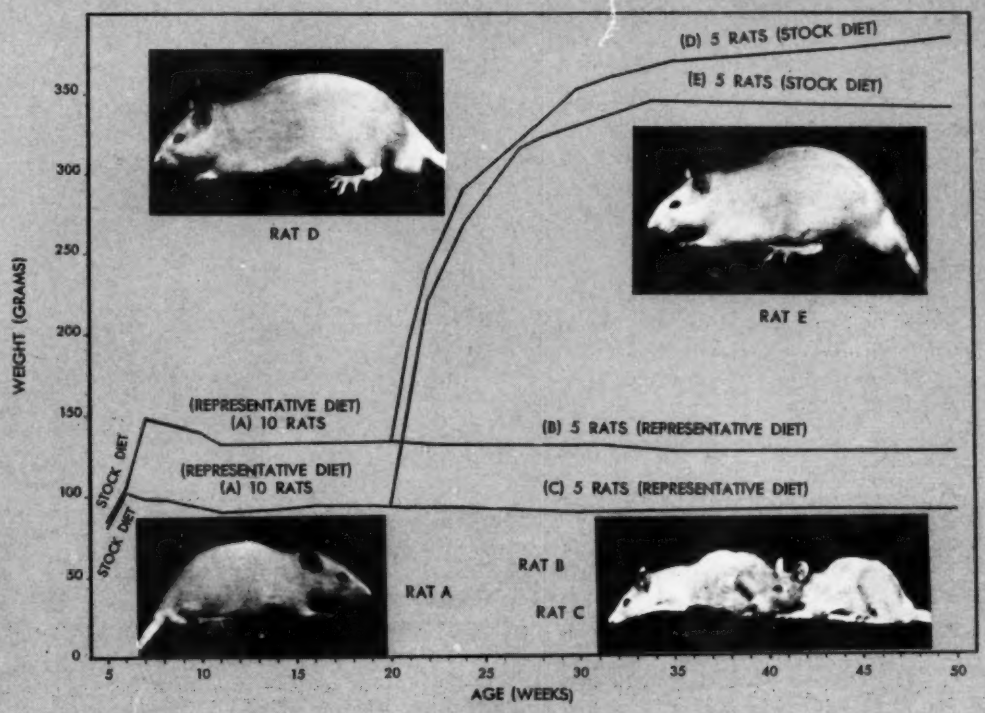



Figure 135

Figure 136

Stock Diet — Age 50 weeks

Basic Diet to Age 40 weeks
Stock Diet to Age 50 weeks

Basic Diet — Age 50 weeks

Stock Diet — Age 37.5 weeks

Basic Diet — Age 11.5 weeks

Basic Diet — Age 11.5 weeks

Stock Diet — Age 7 weeks

Basic Diet — Age 7 weeks

Basic Diet — Age 7 weeks

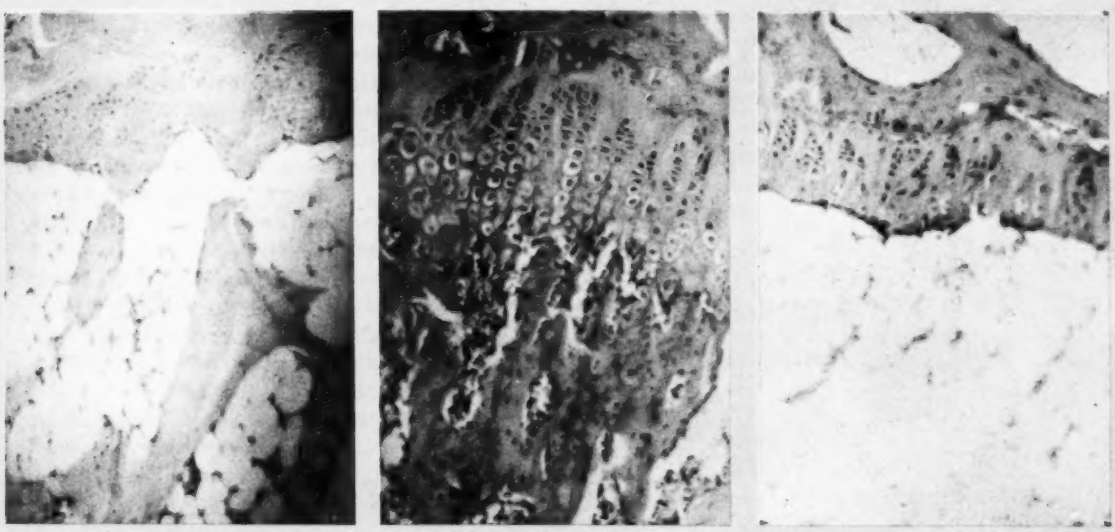
**The effect of the replacement of basic diet by stock diet on the roentgenographic appearance of the distal ends of the radius and ulna.**

After demonstrating the efficacy of folic acid in relieving nutritional macrocytic anemia, macrocytic anemia of pregnancy and nontropical sprue in Alabama, we initiated our work in Cuba and Puerto Rico. Starting in 1945, Mrs. Myrtle Neblett obtained dietary histories covering the period preceding illness and including its entire course. From these data, Miss Jean Grant devised a representative diet, and Drs. Angulo and Spies tested the foods for folic acid content. Many patients with sprue were given this diet, and none had a spontaneous remission while restricted to it. It served for control.

This diet is high in carbohydrates and fats and low in proteins and vitamins, and is important in the natural development of sprue in the Caribbean area and perhaps in many other tropical areas of the world. Jean Grant, Hady López, Margarita Cimadevilla, Luisa Enciso and Mrs. Gilbert Smith obtained these foods and combined them in the same proportion as in the diets of the patients. They were then dried and fed to young white rats at a proper relative level of weight.

Figures 135 through 138 illustrate the arrested skeletal and somatic growth, priapism, testicular atrophy, arrested spermatogenesis and alopecia in the young male albino rats restricted to a basic diet of the type generally eaten by patients with endemic sprue in the Caribbean area.

Figure 137 The Effect of the Replacement of Basic Diet by Stock Diet on the Distal Epiphysial Cartilage of the Radius

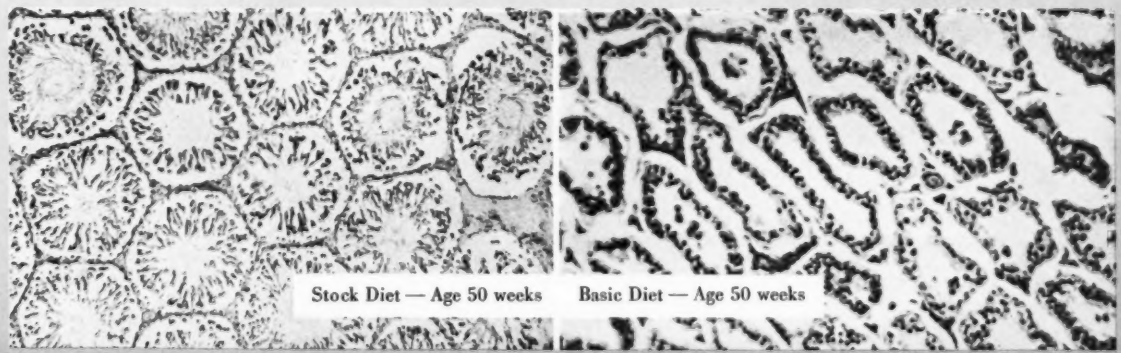


Stock Diet — Age 50 weeks — x175

Basic Diet to Age 40 weeks
Stock Diet to Age 50 weeks — x175

Basic Diet — Age 50 weeks — x175

Figure 138 Comparative Effect of Basic and Stock Diets on Spermatogenesis



Stock Diet — Age 50 weeks

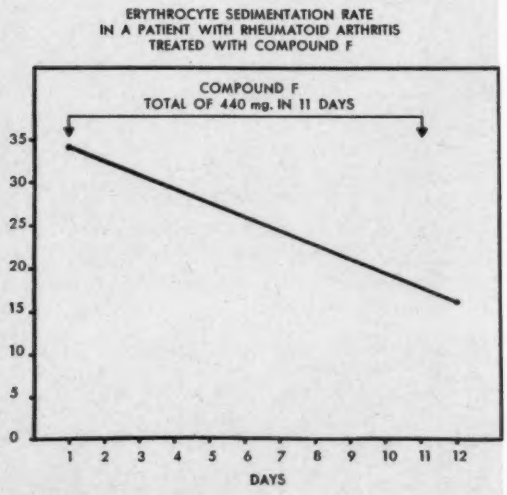
Basic Diet — Age 50 weeks

## ADRENOCORTICAL THERAPY

For more than 20 years we have studied anemia associated with arthritis, and for many years the general nutritional and metabolic aspects of arthritis. These investigations have included the metabolism of salicylates and their effect or lack of effect on the electrolytes, and the effect of pituitary ACTH, cortisone and compound F. In properly selected patients any of these substances will relieve painful, swollen joints and reduce the erythrocyte sedimentation rate. There still is much to be learned about proper dosage levels and methods of administration. We also have studied various mixtures of these compounds, including a recent one furnished by the S. E. Massengill Company, each tablet of which supplies the following: cortisone acetate, 2.5 mg.; sodium salicylate, 325 mg.; aluminum hydroxide gel, dried, 130 mg.; calcium ascorbate, 65 mg., and calcium carbonate, 65 mg.

In many instances we have given one therapeutic remedy which produced amelioration of symptoms, then stopped treatment. If the patient relapsed to the same degree as before treatment, we then started another type of treatment. A brief illustrative case best shows how pituitary ACTH, cortisone, compound F, and a mixture of cortisone with salicylates each produced a similar response in a selected patient.

Figure 139



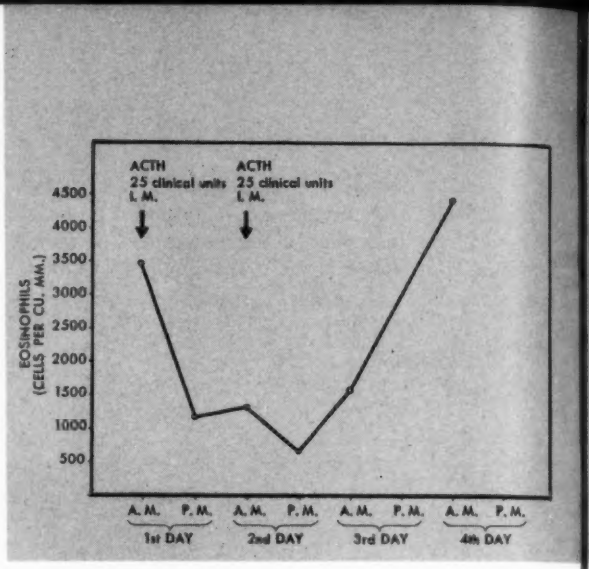




Figure 140

A 58 year old white man came to us with severe rheumatoid arthritis affecting chiefly the hands, elbows, knees and ankles, which had begun about 10 years previously and gradually increased in severity until he was disabled. The joints were swollen and painful. Because he could not open his hands, he had difficulty dressing and eating and could not drive a car. The pain and stiffness in his ankles and knees made walking difficult. The administration of 10 mg. of compound F orally every four hours gave him profound relief. The swelling and pain decreased and he could drive a car and walk with ease. The erythrocyte sedimentation rate decreased promptly (figure 139). A month after therapy with compound F was discontinued, symptoms began to recur and the erythrocyte sedimentation rate gradually increased. He was given a mixture of salicylates and cortisone, several tablets daily. The erythrocyte sedimentation rate slowly decreased and his symptoms gradually were relieved.

Relatively few patients with arthritis have a high eosinophil count, but we have seen a few, such as the following two whom we shall describe briefly.

A 60 year old white woman complained of arthritis and asthma. For six years she had been crippled by arthritic involvement of the wrists, elbows, knees and ankles. She had been told to "live with" her asthma and to make the proper psychic adjustment. The involved joints were

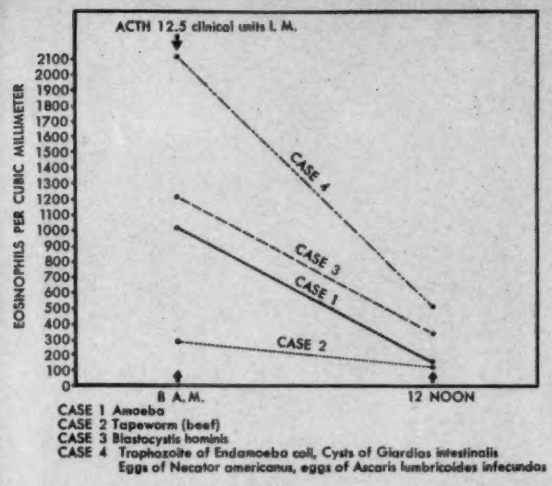



Figure 141

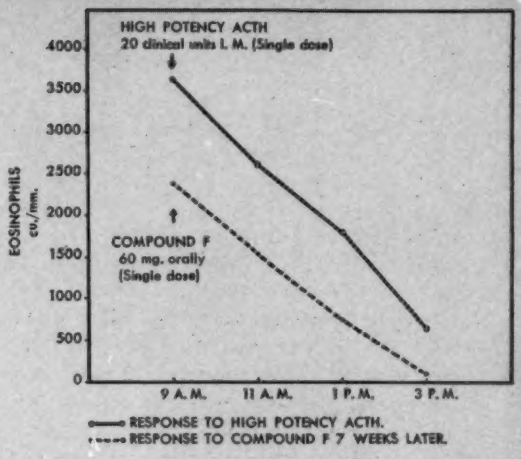



Figure 142

painful, and repeated studies showed an average erythrocyte sedimentation rate of 43 mm. per hour. In 10 laboratory determinations the eosinophils were never less than 25 per cent of the total circulating white blood cells. Figure 140 shows the effect of ACTH on circulating eosinophils. Later she was given 15 clinical units of ACTH intramuscularly every six hours for four days. Eighteen hours after the first injection, her pain was greatly relieved and strength and appetite increased markedly. Her asthma cleared.

In our experience, asthma will not "just disappear" with time, and we see no reason why such patients should not have relief. We instruct them in how not to become pulmonary cripples and how to avoid offending substances. When the usual measures fail, we do not hesitate to try antihistaminics judiciously. If necessary, we give ACTH, cortisone or compound F.

ACTH and compound F do not always lower the circulating eosinophils as profoundly in other conditions. As a general rule, however, the eosinophils do decrease, as shown in figure 141, illustrating the effect of ACTH in cases of parasitic infestation.

The comparative effect on the circulating eosinophils of ACTH and compound F given at a sufficiently high dosage level to a patient with rheumatoid arthritis who also had a high eosinophil count is shown in figure 142. This patient's knees are shown in figures 143 and 144. The swelling and pain are relieved by the local injection of compound F. Local injection has no demonstrable effect on the circulating eosin-

Figure 143

Figure 144

ophils, although within a few hours after the injection his pain is relieved considerably, the knees are decreased in size, and he is able to move them. Compound F injected locally in amounts of 25 to 50 mg. produces no demonstrable systemic change.

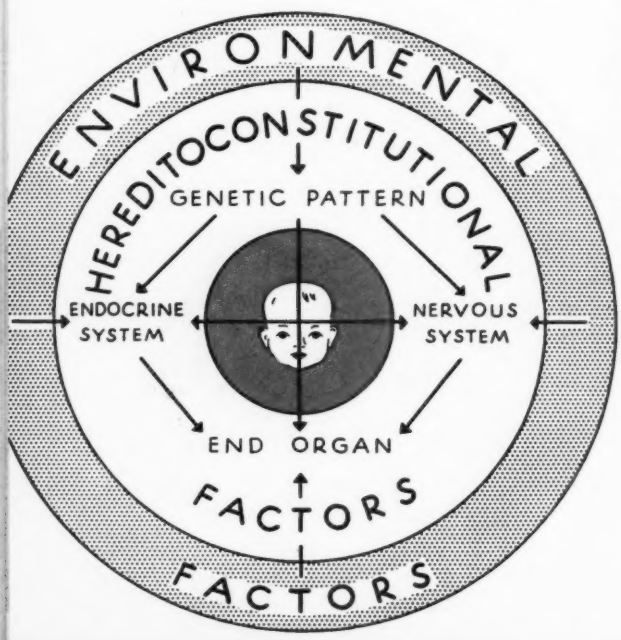
One of the great scientific achievements of recent years is the beneficial effect of local application of cortisone acetate and hydrocortisone acetate in certain ocular diseases. The eye inflammation shown in figure 145 was relieved promptly first by a suspension of cortisone acetate dropped in the conjunctival sac. Many weeks later, when inflammation recurred, similar relief followed the use of an ophthalmic ointment containing hydrocortisone acetate.

Figure 145

## GROWTH AND REHABILITATION

The diagram below illustrates the factors influencing human growth and summarizes the role of nutrition and metabolism in the steady progression from a fertilized egg to an adult human being.

Figure 146 is a photograph of three children, each seven years of age. The one on the left is a few weeks older than the one in the middle, who, in turn, is a few weeks older than the one on the right. From left to right, these children represent improper nutrition, normal growth and development, and precocious advancement of secondary sex characteristics and associated growth phenomenon. It is striking that their body proportions are relatively the same. We already have spent several years studying these children and expect to study them for many more years.




In nutritive failure in infants, children or adults, our objective always is to restore needed nutrients to the body cells. When the patient has nutritive failure and the clinical syndromes of sprue, beriberi, pellagra, riboflavin deficiency, scurvy and certain macrocytic anemias, a practical way of doing this is to administer a basic formula for oral therapy; that which follows is one we use for adults:

| | *Daily* |
|---|---|
| Folic acid | 10 mg. |
| Thiamine | 10 mg. |
| Niacin amide | 150 to 500 mg. |
| Riboflavin | 10 mg. |
| Ascorbic acid | 150 to 500 mg. |
| Vitamin $B_{12}$ (and a potent intrinsic factor) | 5, 10 or 15 µg. |
| Pyridoxine | 10 mg. |
| Calcium pantothenate or panthenol | 10 mg. |

(Pantothenic acid, calcium pantothenate and panthenol have essentially the same effectiveness, molecule for molecule.)

Figure 146

Biotin should be considered for therapy when there is a severe disturbance of the gastrointestinal flora, but no recommendations are made.

From 25 years of concentrated study we have learned that there are four essentials for successful therapy in nutritive failure. One of these is the administration of the basic therapy listed above. The other three are (1) *diet* (4000 calories, 120 to 150 gm. protein, rich in vitamins and minerals); (2) *additional medication* (synthetic vitamins as indicated, orally or parenterally); (3) *natural B complex* (brewer's yeast or extract, and/or liver extract orally or parenterally).

The woman shown in figure 147 was referred to us when she was 20 years old, and as you can see, she looked every day of it. She had lost 40 pounds in four years, had become morose and refused to see her friends. Following a change of diet and dietary supplements, she began to gain weight. She had no specific diagnosable deficiency disease, but her general health improved and her appearance was as shown on the right in figure 147. Her personality changed remarkably, and in a few weeks she began to help with the housework and later she obtained work as a salesgirl.

The man whose illness is portrayed in figures 148, 149 and 150 had worked in a cotton mill for 28 years. His age is uncertain, but some

Figure 147

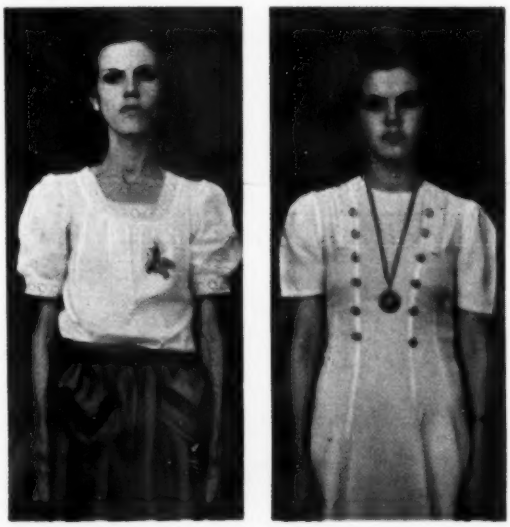


Figure 148 REHABILITATION OF C.H.

Figure 149

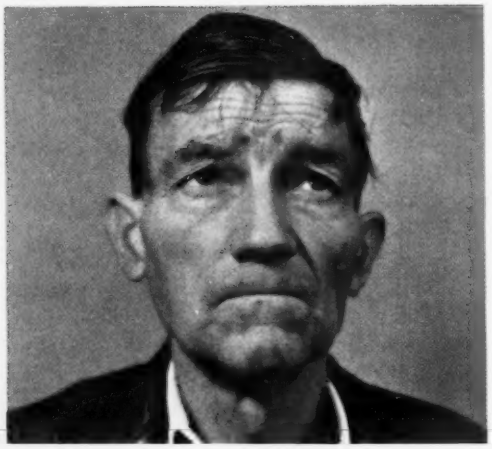
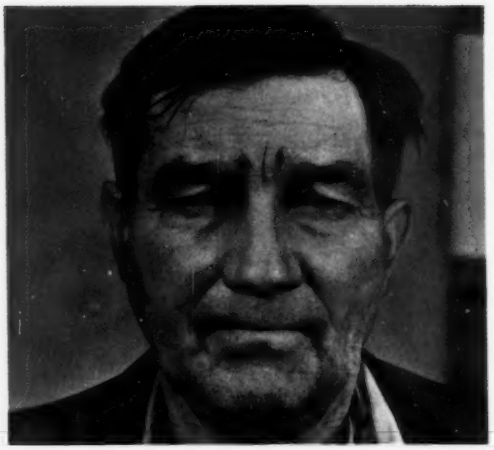


Figure 150



people felt he was on the threshold of senility: "It was impossible for him to get along with other workers and with his family." His family lost their home when he left and went to live in a cave. When found there, he was irrational. He had paranoia and ideas of persecution and was armed. Our workers found him in a confused, somewhat emaciated condition as shown in figure 149. They persuaded him to come with them for observation and treatment. He responded dramatically to the application of the "four essential principles" (figure 150) and has worked steadily in the cotton mill for the past seven years. In his spare time, he has built his present home, shown in figure 148. This man is an example of persons who can be helped to live useful lives and avoid wasting their talents and working capacities.

*In conclusion,* we wish you to know that we take a hopeful view of a direct attack on disease. We believe that diseases are chemical in origin and that they can be corrected. We as physicians must do something about our medical responsibilities, so let us close with the words of the Biblical physician St. Luke, "Let us talk no more of age and death."